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Female Biology, 2nd Edition

FEMALE BIOLOGY, 2ND EDITION

JENNIFER DEVER

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ACKNOWLEDGEMENTS

I would like to acknowledge and celebrate the remarkable achievements of the countless talented female researchers whose dedication has significantly contributed to improving our world. This Is An Open-Access text made available and free to all and in doing so I have relied on my friends colleagues and family to edit the text and support this endeavor. I would like to acknowledge Dr. Elizabeth Richards, Dr. Christina Tzagarakis-Foster and most especially my wife Sara Sollway, and mother June L. Dever for their valuable input. I would also like to thank my students both past and future who have inspired me as a professor.

What is Female Biology?

Over twenty years ago I developed a course for the upper-level biology major at the University of San Francisco called Female Biology. This was from what I perceived as a gap in the undergraduate biology curriculum- students were not learning about the evolutionary aspects of being female and studying the specific health-related issues unique to women. The information in the most widely used general biology textbooks written from a male perspective, focuses on research gained from male models by work conducted in male-led laboratories. This problem still exists. Women need greater representation in biomedical research, increased leadership roles in academia and healthcare as well as equitable pay.

The focus of the course is on the evolution of the female sex and the unique biological aspects of the female sex. There is also an emphasis on the inequities experienced by females as pertains to their health. Additionally, an effort is made in this course to recognize disparities in healthcare across marginalized female and transgender populations.

Why a Textbook on Female Biology?

Numerous higher education textbooks on women's health, genetics, and evolution already exist, but none combine these important subjects. I have written a book that attempts to incorporate these subjects like other biology textbooks. This is a female-centered text whenever possible and highlights women scientists (past and present). I hope to increase students' understanding of female biology, produce more well-rounded biology graduates, and perhaps inspire more young women to become scientists.

The topics examined here tackle what it means to be biologically female framed by evolutionary science. I designed the text for students majoring in biology who have already taken a first-year biology course. With a basic background in general biology, the reader should be able to understand the topics covered in this book.

Each chapter includes

- Student learning outcomes to help frame the concepts covered in each section.
- Think-pair-share questions and deeper discussion questions are designed for small group work to engage students directly.
- A list of key terms covered in the chapter.
- Suggested readings and interesting podcasts to better understand the topics covered.

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This is where you can write your introduction.

1.

EVOLUTION OF SEX

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Explain the link between meiosis and sexual reproduction
- Recall how crossing over increases genetic diversity
- Identify the different types of gametes
- Explain why anisogamy is much more common than isogamy
- Illustrate how oogenesis results in a significantly larger gamete
- Recall how anisogamy can be used to define biological sex
- List the costs of sexual reproduction
- Identify the paradox of sex
- Contrast the two main hypotheses for the evolution of sex

Miriam Menkin's big discovery

Working as a technician on fertility research in Boston at the Free Hospital for Women, headed by clinician John Rock, Menkin (pictured below) made an incredible discovery. Miriam Menkin was the first scientist to successfully fertilize a human egg in vitro (Rock and Menkin 1944). It was the culmination of over six years of working diligently in the lab and although she was the one who did both the intellectual and technical work, as reported in the book by Marsh and Ronner (2019). Her male collaborator, Rock, went on to national prominence while she remained unknown. Forced to relocate to North Carolina when her husband lost his job at Harvard, her research was stopped. Without Miriam in the lab, Rock pivoted from working with IVF and focused his work on the birth control pill. A few years later she returned, however, she was relegated to the position of "literary assistant" editing Rock's articles (Rodriguez 2015).

Photo of Miriam Menkin with her daughter in the lab, [source Harvard University](#).

She was a scientist, with a scientist's mind, and a scientist's precision. — Margaret Marsh

(image via Harvard University)

Photo of Miriam Menkin with her daughter in the lab, source Harvard University.

Observing the fertilization of a human ovum must have been exhilarating. However, the actual process of fertilization was first studied by Derbès (1847) in sea urchins. Artificially exposing eggs to sperm, Derbès observed that only eggs exposed to sperm could be fertilized. Nearly 30 years later Hertwig (1876) documented the act of fertilization in the sea urchin in great detail, noting that eggs and sperm each have their own nucleus. A year later, Fol (1877) described the penetration of an egg by a sperm whereby the two nuclei fused and formed a zygote. Fol's observations of fertilization led him to deduce that the substance present in the nucleus, which he named nuclein, our DNA, was reduced in content by half in eggs and sperm and was therefore responsible for the transmission of hereditary characteristics. It took another 67 to confirm this prediction by Avery, Macleod, and McCarty (1944) who published their findings that DNA is the genetic material rather than protein. Just recently AI has been used to better understand how sperm locks onto the surface of an egg during fertilization (Deneke et al., 2024).

In most sexually reproducing species, including humans, females have distinct biological and physiological features and functions that are essential for the process of fertilization, a critical step in sexual reproduction. Let's examine what sexual reproduction is, how it is related to biological sex, and why it occurs in most multicellular species.

Sexual reproduction vs. asexual reproduction

One of the main characteristics of life is reproduction, the process by which a living organism produces offspring. There are two general ways organisms can reproduce: sexually or asexually.

Defining asexual reproduction

Many single-celled organisms, several plants, and a few multicelled animals can produce offspring without having to find a compatible mate. In asexual reproduction offspring result from the division of duplicated genetic material that produces a clone of a single parent. The offspring are genetically identical to the parent. If there is any variation between parent and offspring it is due to mutation. It is thought that the earliest eukaryotic species were single-cell forms that reproduced asexually through the process of cell division (Wilkins and Holliday 2009).

The specific types of asexual reproduction are apomixis and automixis, for a complete review see (Hojsgaard and Hörandl 2019). **Apomixis** is common in plants and daughter cells are produced from maternal tissues of the ovule. The daughter cells are produced from a modified cellular division process, without fertilization, and have the same chromosome number and content as the parent cell.

Automixis involves the division of the nucleus that creates sex cells with half the genetic content known as gametes that are used for self-fertilization. The gametes fuse so the offspring are not identical clones. The fusion of two gametes created from the same individual does produce some variation however they are much less genetically diverse than if they were created via sexual reproduction.

Some animals such as whiptail lizards in the genus Aspidoscelis reproduce asexually through parthenogenesis, a type of apomixis in which offspring develop from an unfertilized egg. However, in many cases (as with whiptails) species that reproduce parthenogenetically also engage in sexual behavior (Crews and Fitzgerald 1980).

Defining sexual reproduction

🎵“Let’s talk about sex baby”… 🎵-Salt-N’-Pepa

Most animals reproduce through sexual reproduction. Sexual reproduction involves an individual finding a compatible mate. Together as parents, these individuals each contribute half of their genetic material to produce new individual(s) known as offspring. An important feature of sexual reproduction is that the offspring are genetically different from each parent. To accomplish such a feat specific cells that contain half of the DNA from each parent are needed, called haploid gametes, symbolized as n. The gametes fuse during fertilization to create a full genetic complement, called diploid symbolized as 2n, in the offspring. This is referred to as syngamy which results in a genetically unique zygote the result of the fusion of two different gametes.

Question: Which came first, the chicken or the egg?

The egg came first

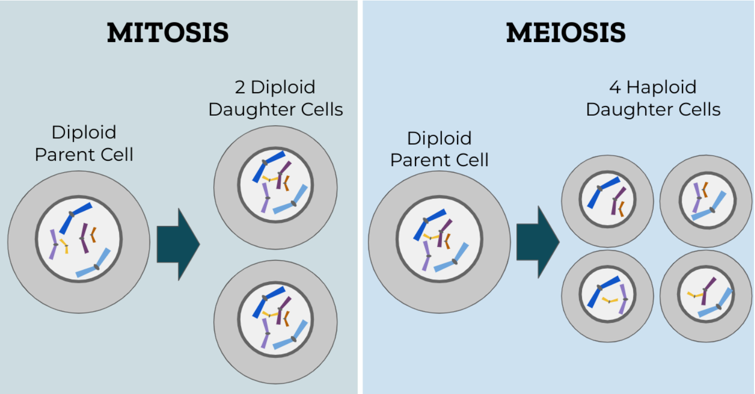
As Samual Butler once said: “A hen is only an egg’s way of making another egg.” Individuals produce specialized sex cells each containing half of the individual’s genetic component, known as haploid gametes. In 1885 evolutionary biologist August Weismann studied horse roundworm eggs and concluded that these specialized cells were transmitting a substance that was somehow connected to observable traits in the next generation (Weismann 1885). He postulated the existence of "germ cells", also known as gametes, contributing half of the genetic material to the next generation. However, it took some time to understand just how gametes were formed through meiosis.

Meiosis produces gametes

Meiosis produces gametes but mitosis was discovered first by Flemming (1882) and we now know that mitosis evolved before meiosis (Wilkins and Holliday, 2009). Mitosis is the mechanism whereby multicellular organisms make more cells for growth and maintenance. The nucleus and cytoplasm of a parent cell divide creating two identical daughter cells, each having the same **diploid number (2n)** of chromosomes as the original parent cell. The goal of mitosis is straightforward: mitosis properly distributes replicated chromosomes into two genetically identical daughter cells. These new identical daughter cells are necessary for the growth and replacement of damaged cells.

Meiosis is similar to mitosis but occurs only in the germ cells (highly specialized cells that form gametes) and involves two successive divisions (MI and MII) allowing for the reduction division of chromosomal content. The new daughter cells have the **haploid (n) number of chromosomes** and are **gametes**.

For example, a diploid human somatic cell contains 46 chromosomes but a haploid gamete cell (egg or sperm) contains only 23 chromosomes (n = 23). Below is a diagram comparing daughter cells produced in mitosis versus meiosis.

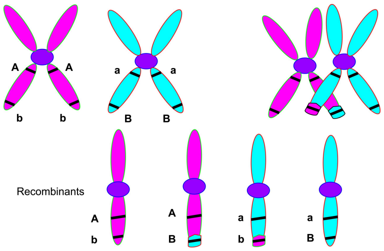

MITOSIS
Diploid Parent Cell
2 Diploid Daughter Cells
MEIOSIS
Diploid Parent Cell
4 Haploid Daughter Cells

Comparison of mitosis and meiosis in a diploid cell with three chromosomes.

Haploid cells (n) are produced from a cell that was originally diploid (2n). Recall that the cell cycle has four stages, G1, S, G2, and M. During the S phase the DNA is replicated and then packaged into chromosomes at the start of the M phase of the cell cycle. It is during the M phase that nuclear division and cytoplasmic division occur. For a detailed description of meiosis see [Meiosis: An overview of key differences from mitosis](#)

Homologous chromosomes pair up and synapse during prophase I of meiosis. Crossing over between non-sister chromatids creates new allelic combinations.

During the M phase of the cell cycle, the chromosomes in the diploid parent cell undergo alignment and division. Initially, two sets of matching chromosomes contain the same genes, but potentially different alleles, which are called homologous chromosomes. During the first stage of meiosis, prophase I, homologous pairs of chromosomes come together allowing for proper alignment of the chromosomes. Proper alignment is necessary for the equal division of the genetic material. This also enables another important event during meiosis known as crossing over. **Crossing over** (shown in the figure below) is the physical exchange of chromosomal segments between different chromosomes within the homologous pair. This creates new combinations of alleles that contribute to the uniqueness of the zygote. Crossing over, depicted in the diagram below, is also referred to as recombination.



Homologous chromosomes pair up during MI and crossing over occurs producing recombinant chromosomes.

How the chromosomes pair up is random- the maternal chromosome can be on the left of the paternal chromosome or vice versa. With many pairs of chromosomes the random alignment of each results in the independent assortment of genes on different chromosomes. The first physical evidence of different chromosomes assorting independently during meiosis was provided by female geneticist **Estrella Eleanor Carothers** who examined grasshopper chromosomes during meiosis (Carothers 1917). Unlike mitosis, which only has one division, meiosis has two nuclear divisions (MI and MII) producing four daughter cells. These four haploid daughter cells are genetically unique from each other because they contain only one homologous chromosome from each pair that has undergone crossing over. This is observed among algae in the genus *Chlamydomonas* . These single-celled organisms undergo meiosis and produce distinct gametes that are genetically unique with different chromosome types. When they mate, one contributes a + type, and the other a – type. These fuse and create a diploid product (+/-) that differs from each parent.

There are a variety of sexual life cycles in eukaryotes, some are **haplotonic** (the haploid cell undergoes mitosis, eg. algae); **diplotonic**, (the diploid phase undergoes mitosis, eg. most multi-cellular animals and seed plants; and **diplohaplotonic** (both undergo mitosis, eg. alternation in generations in some plants). The more complex the organism, the more likely the diplotonic cycle is the case (see review by Heesch et al., 2021).

Meiosis and the transmission of hereditary traits

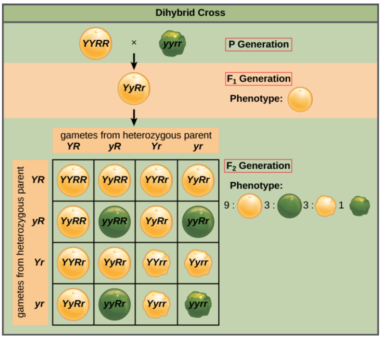
Gregor Mendel (1866) presented his results in the paper “Experiments on plant hybridization” before the discovery of either meiosis or chromosomes. However, he was able to use experimental crosses of pea plants to deduce each parent has two "factors", also known as alleles that make up their genotype for each trait. Each of the two parents randomly contributes one of those alleles to their offspring in the next generation. Mendel meticulously crossed seven different sets of pure-breeding pea plants for a single trait or phenotype (each exhibiting two distinct forms, e.g. plants with green pods x plants with yellow pods) which produced offspring that only had green pods. Because all the offspring were green he considered the green pod the "dominant" phenotype. Mendel then self-crossed the green pod first-generation offspring to produce a second generation. This resulted in a consistent pattern of ¾ exhibiting the "dominant" (green) phenotype to ¼ exhibiting the "recessive" (yellow) phenotype.

- **Parent generation (P): Green pod x Yellow pod**
- **First generation (F1): All Green pod**
- **Second generation (F2): ¾ Green pod; ¼ Yellow pod**

This pattern was consistent for each of the seven traits in Mendel's crosses. Thanks to the large sample size produced from each of the crosses, Mendel was able to mathematically explain the results, concluding that when the parent plants were crossed this was a monohybrid cross, they each had different alleles, represented by letters (e.g. GG and gg) that they passed to the F1 plants (Gg). The F1 plants produced egg and sperm cells that exhibit the "law of equal segregation". Equal segregation means that each parent has two alleles per trait (Gg) but they only pass on one allele per trait (G or g), and they have an equal chance of passing along either one to the next generation. This is possible thanks to meiosis. Each parent's diploid chromosomes divide and segregate equally into their haploid gametes.

When Mendel considered two traits together in a dihybrid cross, e.g. green pod and tall plant, (genotype *GGTT*) by a yellow pod, short plant. (genotype *ggtt*), he demonstrated that the factors for different traits are not connected and are randomly passed onto the next generation. Once again his results were consistent for all seven traits in dihybrid crosses. He called this the "Law of **Independent Assortment**" and was correct because fortunately each of the alleles for these traits is located on different chromosomes. The **9:3:3:1** phenotypic ratio observed in the second generation is a product of two different alleles on different chromosomes aligning randomly during meiosis. The Punnent square below illustrates how the second-generation phenotypic ratio is obtained.

- P: Tall plant with green pods x Short plant with yellow pods
- F1: All Tall plants with green pods
- **F2: 9/16 Tall, Green; 3/16 Short, Green; 3/16 Tall,Yellow; 1/16 Short, Yellow**



	YR	yR	Yr	yr
YR	YYRR	YyRR	YYRr	YyRr
yR	YyRR	yyRR	YyRr	yyRr
Yr	YYRr	YyRr	YYrr	Yyrr
yr	YyRr	yyRr	Yyrr	yyrr

Dihybrid cross between yellow, round heterozygous F1 offspring results in an F2 generation with a 9:3:3:1 phenotypic ratio.

At the time Mendel's research was published it went unnoticed however it was rediscovered 35 years later by William Bateson (1901) who went on to coin the term "genetics". Soon after a direct link between cytological evidence (actual chromosomes viewed under the microscope) and Mendel's principles of equal segregation and independent assortment was made. Working with grasshopper chromosomes, Sutton (1902) established the fact that chromosomes are organized into homologous pairs dividing equally in the first phase of division and then reducing the chromosome number in the second phase of division. He went on to put forth the chromosome theory of inheritance (Sutton 1903).

Theodor Boveri (1904) observed chromosomes actually dividing when gametes were made in roundworms (*Ascaris*), further supporting the conclusion that the chromosomes were the location of Mendel's hereditary factors. The confirmation of the chromosomal basis of inheritance was provided by Thomas Hunt Morgan (1911) and his student Alfred Sturtevant (1913) in genetic experiments with the common fruit fly (*Drosophila melanogaster*). Together they were able to show that genes are located linearly on chromosomes and a locus represents a specific position or site on a chromosome where a particular gene is located. Later researchers were able to demonstrate that genes consisted of DNA. A brief overview of DNA and genes is provided in the following chapter, the Genetics of Sex.

Why are there only two types of gametes (eggs & sperm)?

A brief review of the theory of natural selection

Before we can understand why sexual reproduction is much more common than asexual reproduction, or why there are only two different types of gametes as opposed to several different types we must refresh our memory of evolution and natural selection. **Charles Darwin** reluctantly published “On the Origin of Species” in 1859 because he was so concerned about the cultural impact it would have on society. In this seminal text, Darwin provided a thorough explanation of evolution and a detailed explanation of his theory of natural selection. This was the first evidence-backed explanation of how populations evolve and new species can arise. The image below is of different finches from the islands of the Galapagos archipelago comes from Darwin’s own field notes that resulted from his voyage around the world. Darwin observed variation within populations and he postulated that if such variations are inherited, then they will be "naturally selected".

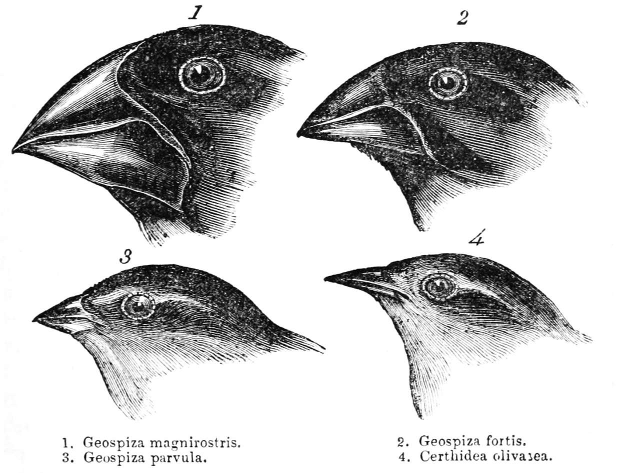

1
2
3
4
1. Geospiza magnirostris.
3. Geospiza parvula.
2. Geospiza fortis.
4. Certhidea olivasea.

Illustration of Darwin's finches. Note the distinct beak shape of each.

The theory of natural selection can be condensed into four postulates

1. Variation exists within populations.
2. The heritable portion of this variation is passed to the offspring.
3. More offspring are produced than can survive and there is competition for

limited resources.

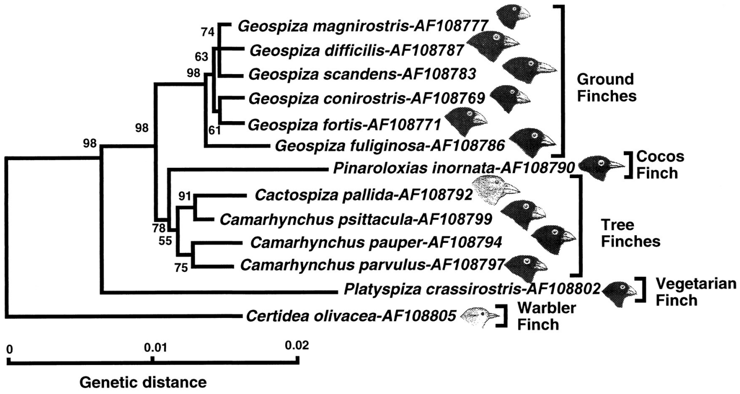
4. Those who have inherited traits that increase their reproductive success (fitness) will produce more offspring in the next generation, and their heritable traits will increase in frequency over time.

The Botsford's Leaf-litter toad hides very well thanks to its adaptive coloration, photo taken by Jodi Rowley.

Evolutionary fitness is directly connected to reproduction. **Fitness** refers to the number of offspring produced by an individual in the next generation and traits such as survival and reproductive success combine to determine fitness. Natural selection for one trait over another occurs "when there is a consistent, average difference in fitness" (Futuyma 2009) thus selection is the evolutionary force that predominately results in **adaptation**. Adaptations are traits that increase an organism's chance of survival. An example of an adaptation is the cryptic coloration found in Botsford's Leaf-litter toad (*Leptolalax* *botsfordi*) pictured on the right, which improves its ability to evade predation in the montane rainforest of northern Vietnam, thereby increasing fitness.

Darwin observed that different species of finches in the Galapagos islands had different shapes and sizes of beaks which he proposed evolved through natural selection. Examination of the phylogenetic tree (shown below) created from the analysis of DNA sequences provides strong support that Darwin's finches are closely related having shared a common recent ancestor (Sato et al. 1999). However, they have diverged due to ecological differences in their environments that impact food availability. For example, the ground finches have larger beaks for breaking seeds and smaller beaks more suited for capturing insects whereas the tree finches have large beaks used for "tearing bark and crushing twigs and small branches…Darwin's finches vary in beak shape/size and are versatile in their feeding habits, see illustration below. This versatility is fostered by ecological opportunity…"(Grant and Grant 2003). This is an example of how adaptations in beak shape increase fitness under particular environmental conditions and are thereby naturally selected over other types.

Selection can be subdivided into different categories based upon outcomes: a) **directional selection** is when one phenotypic trait is consistently favored in a population over time; b) **stabilizing selection** is when the intermediate phenotypic trait is consistently favored within a population over either extreme; and c) **disruptive selection** is when both phenotypic extremes are consistently favored over intermediates.


Geospiza magnirostris-AF108777
Geospiza difficilis-AF108787
Geospiza scandens-AF108783
Geospiza conirostris-AF108769
Geospiza fortis-AF108771
Geospiza fuliginosa-AF108786
Pinaroloxias inornata-AF108790
Cactospiza pallida-AF108792
Camarhynchus psittacula-AF108799
Camarhynchus pauper-AF108794
Camarhynchus parvulus-AF108797
Platyspiza crassirostris-AF108802
Certidea olivacea-AF108805
74
63
98
61
98
98
91
78
55
75
Ground Finches
Cocos Finch
Tree Finches
Vegetarian Finch
Warbler Finch
0
0.01
0.02
Genetic distance

Phylogenetic tree from mitochondrial DNA in Darwin's finches from the Galapagos Islands from Sato et al. 1999.

Darwin proposed that natural selection is the chief cause of evolutionary change. However, **selection is not the only evolutionary force**, mutation, genetic drift, and gene flow also cause changes in populations over time. Keep evolution in mind because it is responsible for many of the features we will discuss throughout this text.

For most species, eggs and sperm are different in size and shape

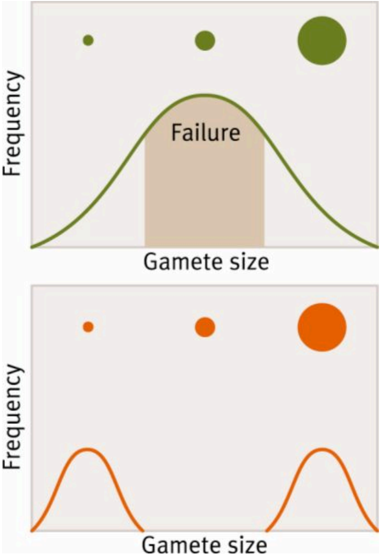
Although most eukaryotic organisms have only two sexes, sexual reproduction does not require *only* two different sexes.

There exist many unicellular eukaryotes, such as protists and fungi, which exhibit **isogamy**. Isogamous species produce gametes that are the same size and shape. They are physically indistinguishable but are distinct self-incompatible genetic "mating types". Often there are two different types designated as + and – like those found in many species of algae such as *Chlamydomonas reinhardtii* (Ferris and Goodenough 1994). However, Lehtonen et al. (2016) report the number can vary (e.g. three gamete types found in *Dictostelium discoideum,* seven in *Tetrahymena thermophila*). These haploid gametes undergo **syngamy** and produce a viable zygote.

In isogamy the parental investment in the zygote is equal. However, isogamy is found only in single-celled organisms which begs the question why? It may be that larger multicellular organisms require greater nutrient storage (Parker, Baker, and Smith 1972). Hanschen et al. (2018) found that species with large eggs and small sperm (**anisogamy**) produce larger zygotes than isogamous species, likely leading to anisogamy evolving from isogamous multicellular species multiple times.

Anisogamy is the predominant system for multicellular organisms and is characterized by two different gamete sizes: small, motile (**microgametes**), and large, immotile (**macrogametes**). Anisogamy likely evolved from isogamous microgametes (Lehtonen and Parker 2014; Lehtonen, Kokko, and Parker 2016). The increased complexity of multicellular organisms would account for the eventual selection of macrogametes which could be large enough to support a more complex zygote.

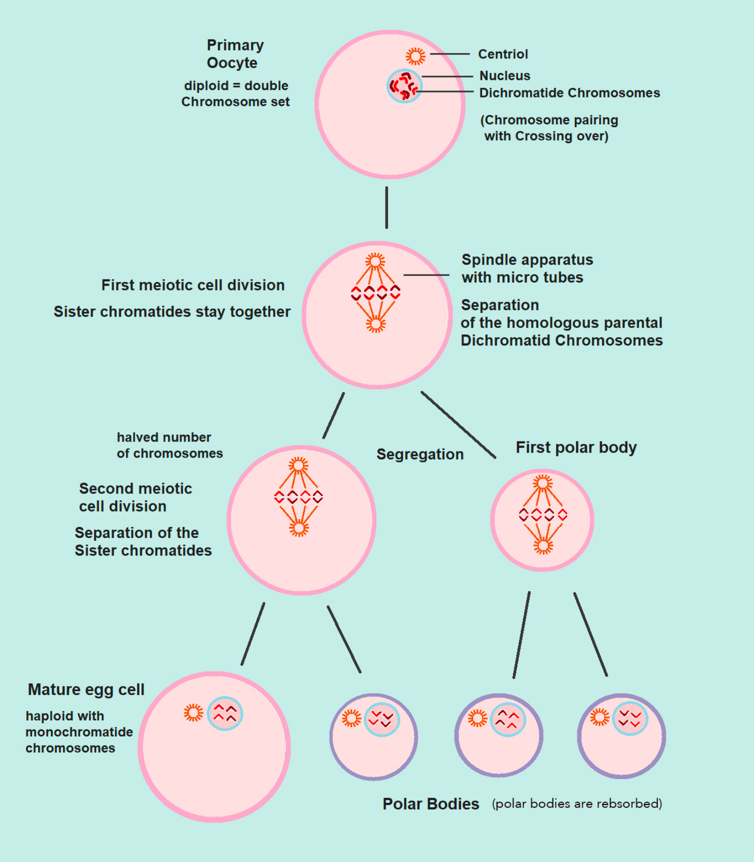
Why anisogamy? Larger eggs can supply greater amounts of nutrients and proteins for the developing embryo. So multicellular organisms under natural selection have only two distinct gamete types (dimorphic gametes) that are winners in the game of gamete evolution. The theory for the evolution of gamete dimorphism first posed by Darwin is based on the trade-off between gamete number and offspring fitness. The main functions of a gamete are to find and fuse with another haploid gamete and produce a successful zygote that will go on to survive, mature, and ultimately reproduce. Gamete competition is a selective force resulting in ever-shrinking gametes that increase in number while simultaneously ever-larger gametes providing nutrients.



Theoretical comparison of different gamete sizes. Intermediate size loses out to both smaller and larger size gametes.

Disruptive selection can explain how two and only two forms are selected (intermediate-sized gametes are selected against) and why smaller gametes favor fusing with larger gametes (Parker, Baker, and Smith 1972). This is illustrated in the diagram to the left. The intermediate size loses because it is neither best at finding other gametes nor best at supporting offspring, one form is favorable for a particular function over another but rarely can you combine different functions into a single form. Therefore gamete dimorphism evolved to increase the likelihood of gametes finding partners which they can successfully fuse (Dusenbery 2002). Small, motile, abundant male gametes increase the chance of finding a partner of the opposite sex when gametes are released into seawater. A larger female gamete encourages a more successful zygote. The microgamete must be able to find the macrogamete, and as larger, allows the macrogamete to emit more pheromones to increase male gamete attraction (Dusenbery and Snell 1995). For a comprehensive review of anisogamy see (Lehtonen and Parker 2014).

We can contrast **gametogenesis** in females and males (oogenesis with spermatogenesis, respectively) and see how **oogenesis** produces a single, large, immotile egg thanks to the unequal division of the cytoplasm in both MI and MII. This creates polar bodies that are reabsorbed, leaving just a single, extra-large egg. But in males, **spermatogenesis** has an equal division of the cytoplasm in both MI and MII producing four equally sized small, motile sperm (image below from Wikipedia. 2023. "Oogenesis" Wikimedia Foundation). The extra cytoplasm in the egg contributes to zygote development following fertilization.


Primary
Oocyte
diploid = double
Chromosome set
Centriol
Nucleus
Dichromatide Chromosomes
(Chromosome pairing
with Crossing over)
First meiotic cell division
Sister chromatides stay together
Spindle apparatus
with micro tubes
Separation
of the homologous parental
Dichromatid Chromosomes
halved number
of chromosomes
Segregation
First polar body
Second meiotic
cell division
Separation of the
Sister chromatides
Mature egg cell
haploid with
monochromatide
chromosomes
Polar Bodies
(polar bodies are rebsorbed)

Oogenesis. During MI and MII the polar bodies are the result of unequal division of cytoplasm. The result is a single, large egg.

Biological Sex Defined by Anisogamy

Medicogram

Humans have anisogamous gametes. The egg is 10,000 times larger than the sperm. Ovum surrounded by significantly smaller sperm.

Although we often think of biological sex as the way to define multicellular organisms as either female or male based on their reproductive anatomy and physiology, it is more useful to look at the gamete size as the true way to define biological sex. Females produce macrogametes that remain stationary and males produce microgametes that move around (Parker, Baker, and Smith 1972); (Bell 1982); (Margulis and Sagan 1986). For example, in humans, the female egg diameter is greater than 0.1 mm, whereas the sperm, with its distinct flagellum allowing motility, has a much smaller size of just 5-7 µm long (pictured to the right). The asymmetry of anisogamous gametes leads to what (Parker 2014) refers to as the "sexual cascade" because it is the key to fundamentally establishing the basis for sexual dimorphism in body shape/size and differences in sexual behavior.

Why did sex evolve?

Asexual reproduction wins over sexual

reproduction when all things are equal.

Asexual reproduction has many advantages over sexual reproduction and can be a highly fit way to reproduce, for example, some species of bdelloid rotifers (see below) have been successfully reproducing asexually for over 40 million years (Nowell et al. 2018). Asexual reproduction is significantly more efficient. It does not require finding a mate or the complex process of meiosis, which takes time and energy. Nor does it pose the obvious risks that mate attraction poses such as potential harm from convincing the mate to be receptive or risking obtaining disease from a mate. It also does not ruin the potentially fit genetic combination of alleles in a way that sexual reproduction does.

John Maynard Smith created a simple model testing the cost of sex (1978) that shows asexual clones multiply twice the rate of sexual entities. In the case of asexual reproduction, all individuals in the population are female and each female produces four offspring, which in turn produce four offspring. With sexual reproduction, two individuals (female and male) produce two offspring (male and female) and thus this asexual population increases at twice the rate of the sexual lineage. Thus, in a competition between asexual and sexual organisms, the asexual ones always outnumber the sexual ones. Several theoretical models and empirical experiments have supported the notion that asexual clones outcompete their sexual counterparts under constant conditions (Hamilton 1980); (Lively 1987); (Jokela et al. 1997).

The paradox of sex

Asexual reproduction has key advantages over sexual reproduction, but, of the one million multicellular animal species identified so far nearly all engage in sexual reproduction rather than asexual reproduction (Speijer et al. 2015). Why is sex so successful despite all its disadvantages? This is a paradox. It is clear that sexual reproduction produces a high level of genetic variation in offspring therefore natural selection favors this mode of reproduction over asexual reproduction. Since sex creates new genetic combinations selection of the more beneficial combinations under changing environmental conditions can increase fitness. Williams (1975) likened life to a lottery with sexually reproducing organisms able to buy multiple tickets compared to asexual organisms that only purchase a single ticket. Under this model, the sexual organisms increase the probability of their future offspring winning (i.e. surviving). But is that enough to cause the widespread obligate sexual reproduction seen in nature?

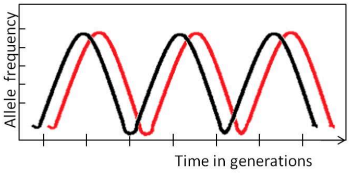
The key benefits of sexual reproduction

- sexual reproduction generates genetic diversity, increasing survival rates under changing conditions, and increasing reproductive fitness, which is defined as the ability of individuals to pass on their genes to subsequent generations;
- sexual reproduction helps rid populations of harmful genetic combinations.

Hypotheses on why sexual reproduction evolved

Red Queen Hypothesis

The Red Queen hypothesis (RQH), put forth by (Van Valen 1973) was inspired by Lewis Caroll's Through the Looking Glass domineering character the Red Queen, who points out to a frustrated Alice, who has been running and running and getting nowhere that "it takes all the running you can do, to keep in the same place". Van Valen was attempting to explain the observed constant rate of extinction supported by the fossil record with this analogy. The forward motion can seemingly get participants nowhere and Van Valen proposed that "every species does the best it can in the face of selection pressures, each species is part of a zero-sum game against other species" and "no species can ever win". This is similar to what happens in coevolution which occurs when two directly interacting species affect one another's evolutionary trajectory (Erlich and Raven 1975). The RQH was first used to explain the evolution of sex by Bell (1982) who noted that with two directly interacting species, sexual reproduction will enable them to coevolve rapidly to keep up with one another. Bell considered how genetic diversity oscillates (in models) in both parties involved in the coevolutionary "arms race" like Van Valen's zero-sum game as illustrated in the diagram below.



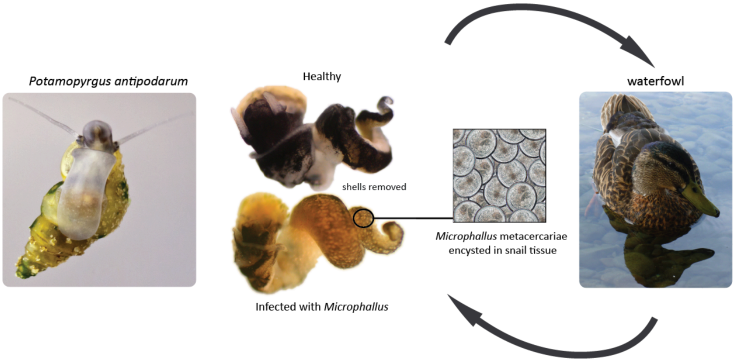
Negative frequency dependent selection in the coevolution of hosts and parasites; black curve: host; red curve: parasite

Coevolution is characterized by reciprocal changes in allele frequencies within populations. Black line represents host, red line represents parasite.

In the case of sexual reproduction, evidence suggests that host-parasite coevolution is a significant driver of sexual reproduction because it rapidly increases genetic combinations which can benefit a host by blocking infection from a parasite and conversely increase a parasite's ability to infect its host (Lively 1996). Anything that decreases the likelihood of a host being infected by the parasite will have a selective advantage, and in turn, the parasite that increases its likelihood of infecting the host will have a selective advantage. This is one example of how interspecific interactions may drive sexual reproduction at the population level. For a more complete review of the RQH see Lively (Lively 2010).

Lively and his colleagues found support for the RQH in multiple experiments involving the New Zealand mud snail infected by a trematode parasite (Dybdahl and Lively 1998) [see below]. Additionally, Daphnia (water flea) and their parasite Pasteuria were studied in lake sediments, showing an increase in genetic diversity and virulence in the parasite over time (Decaestecker et al. 2007). Morran et al. (2011) also showed how sexually reproducing roundworms (Caenorhabditis elegans) were able to persist in the presence of coevolving bacterial (Serratia marcescens) parasites, whereas the asexual C. elegans were not, suggesting that sexual reproduction significantly increased their fitness in the presence of the parasite.

The New Zealand mud snail, *Potamopyrgus antipodarum,* is interesting because members of this species have both asexually and sexually reproducing females in the same populations found in different habitats. This snail is often infected by the trematode parasite in the genus Microphallus which uses a snail as an intermediate for its duck host (see image below). The trematode has a very strong impact on snail fitness, causing sterility in those heavily infected. Lively (1987) found this a great model to ask why sexual reproduction is predominant. Snails inhabiting different habitat types (stream and lake) were genotyped using allozymes, and measurements of parasite infection were used to directly compare sexual forms with asexual ones to see if there were any significant differences. Snails with rare genotypes had an advantage over parasite infection compared to those with more common genotypes. Laboratory experiments with parasite-exposed snails compared to non-exposed dissected control snails showed that once particular genotypes become more common in the population (increase in frequency) they become less resistant to infection. The prediction that sexual females would be more prevalent in sites with greater local parasite load was also supported by more recent research by Amanda Gibson involving the artificial inoculation of wild-caught snails and duck feces from Lake Alexandrina in NZ (Gibson, Xu, and Lively 2016), (image below depicting snail life-cycle from Gibson).


Potamopyrgus antipodarum
Healthy
shells removed
Infected with *Microphallus*
Microphallus metacercariae encysted in snail tissue
waterfowl

The life cycle of the parasite Microphallus is complex, going from snails to duck guts to duck feces back to snails.

Q&A with Dr. Amanda Gibson

Assistant Professor at the University of Virginia

Dr. Amanda Gibson, Ph.D.

What made you want to study the RQH? I first heard about my PhD advisor Curt Lively's work on the Red Queen Hypothesis when I was a freshman in college. My intro bio professor, Dr. Jill Miller, presented some of his data on the snail *Potamopyrgus antipodarum* and its trematode parasites. It wasn't his results that stuck with me, but something Prof. Miller said about the approach of Curt and his lab – that they designed study after study to falsify the Red Queen Hypothesis. They hadn't succeeded yet. So I was intrigued by the way they thought about problems. Once I was in the lab, I think ultimately it was the history of the study of the evolution of sex, and my graduate lab's particular role in that history, that made me want to study the Red Queen Hypothesis. Evolutionary biologists have grappled with the problem of sex for decades now. Researchers generated a flurry of hypotheses to explain why sex is maintained, and Curt is one of the original scientists to compete those hypotheses against one another. I have the impression that no one expected the Red Queen to garner as much empirical support as it has.

It probably helped that in the first year of my Ph.D., Levi Morran, a postdoc in the lab, published a beautiful experiment showing that coevolving parasites can maintain outcrossing in laboratory populations of the nematode C. elegans. That study drove home to me how special parasites are as an evolutionary force – unlike abiotic features of the environment, parasites can reciprocally adapt, so host populations are never evolving toward a fixed optimum; the rules are always changing.

What did you like most about fieldwork?

Fieldwork has brought me to beautiful, remote destinations that I might otherwise never have had the opportunity to visit. My doctoral research took me to New Zealand for six weeks every winter. I lived in a field station in Kaikōura, on the east coast of the South Island, where I found wonderful friends in the staff and researchers there.

Our team visited lakes all over the island to sample snails. Most of my work focused on Lake Alexandrina, where my advisor had studied these snails since 1985. In spending so much time at that lake year after year, working intensively, I got to know my surroundings in a special way. I knew which sites would have lots of snails, which were hard to get to, which had nice banks that were easy to sample, when the weather would make sampling a breeze, and where I'd find tons of parasites. I loved that sense of intimacy with these natural populations. Watching these organisms and environments for so long, I could tell what changed, and what stayed the same. That grounding in the field pointed me in the right direction as I tried to make sense of my data and helped me find the next question.

What did you find to be the most difficult thing about getting a PhD? Balance. I took 6 years to get my Ph.D., but I felt like it blew by. Each semester and each field season was packed with things I wanted to do. I loved that sense of excitement and urgency – it kept me motivated – but if I did it again, I would have set aside more time for the many other aspects of my life that I value.

Moving on is hard too! You become a real expert in your specific area during your Ph.D. I gained a lot of confidence as a scientist. Then, suddenly, you move on to your next thing, and it can feel like you're starting over. I felt rejuvenated by learning new things in my postdoc, but I also found it difficult to step out of what had become my comfort zone and lose some of the momentum I'd had.

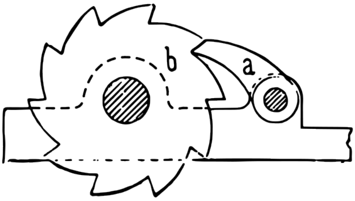
What do you enjoy most about your job now? Working closely with my students and trainees and watching them grow into independent, confident scientists. They raise questions and hypotheses that I know I would not have arrived at on my own, they have become experts in concepts or techniques that are totally new to me, and they regularly figure out how to do things I didn't think were possible. I love that, as their advisor, I always get to be on their team.

Muller's Ratchet Hypothesis

Mutations occur spontaneously and harmful ones can accumulate in the genome over time. Herman Muller (1964) recognized the implications of the accumulation of harmful mutations in asexual lineages over time and developed the analogy of a mechanical ratchet (a mechanical device that rotates in a single direction, preventing movement in the opposite direction, shown in the figure below). As each harmful mutation emerges the ratchet increases the mutational load and pushes an asexual organism closer to the inability to reproduce or even die. Experiments involving bacteriophage, ciliates, and *E. coli,* have all shown an increase in harmful mutational loads (Lin-Chao, Chen, and Wong 1992); (Lynch and Gabriel 1990); (Lenski 2017). Muller proposed the hypothesis that sexual reproduction evolved because it can reverse the "ratchet's effect" by creating new genetic combinations, thereby purging harmful mutations. Thus sexual reproduction may be advantageous, particularly in small populations. Multiple models and computer simulations support this, particularly when they involve synergistic interactions (Hadany and Comeron 2008).

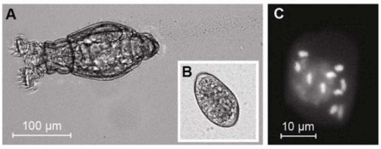
Limitations of Muller's hypothesis

Sexual reproduction did not evolve from a single event, more likely it evolved independently numerous times. Margulis and Sagan (1986) contend a "series of historical accidents" resulted in meiotic cell division and that "selection has favored sexual organisms, but not because they were sexual". Multiple mathematical models using unrealistic assumptions such as infinitely sized populations isolated from others under constant selection and experimental tests have involved over-simplified parameters (Otto and Lenormand 2002). Improved models would simulate realistic populations, incorporate more complex conditions, and account for randomness (Liow, Van Valen, and Stenseth 2011). For example, when recently testing the RQH MacPherson, Keeling, and Otto (2021) actually observed a decrease in genetic variation when they modeled host-parasite coevolution in a finite population rather than the



Muller's ratchet figure is used to depict how harmful mutations accumulate through asexual reproduction. The ratchet only goes in one direction but sexual reproduction breaks this pattern through the rapid incorporation of new alleles.

expected increase produced by frequency-dependent selection.



The bdelloid rotifer *M. quadricornifera*, an unhatched egg and metaphase nucleus.

Bdelliod rotifers (image on the left from Laine et al. 2020) comprise over 450 distinct species that inhabit freshwater ponds and lakes worldwide. They can survive under extreme conditions of starvation, extreme temperature, and prolonged desiccation by going dormant. Entire populations are all female, so it was thought they reproduced solely through apomixis. The diversity observed in these rotifers was hypothesized to come from horizontal gene transfer (the direct uptake of genes from other species). However, Veronika Laine and colleagues found strong support in their genome evolution for the hypothesis that these rotifers reproduce sexually on rare occasions. Laine, Sackton, and Meselson (2022) show that these rotifers are sexual only when it is essential, but the RQH cannot explain why they continue to reproduce sexually because “Bdelloids gain freedom from having to co-evolve with biological antagonists by their ability to survive prolonged starvation, extremes of temperature and exposure to toxic conditions lethal to other taxa”. The evolution of sex is likely much more complicated than either of these hypotheses can explain.

Q&A with Dr. Veronika Laine, Ph.D.

Postdoctoral Researcher at the Finland Museum of Natural History

Dr. Veronika Laine, Ph.D., photograph by Riikka Campomanes.

What drew you to using genomics to answer evolutionary biology questions? I have always been interested in how different species adapt to changing environments and which genes play a part in adaptation. I especially want to link the molecular changes to individual phenotypes to population and ecosystem levels. Since I am also a computer geek, the technology and tools used in genomics make the field really interesting and always evolving. There are always new tricks to be learned.

What did you find to be the most difficult thing about getting a PhD? I think the most challenging part was project and time management. Especially during the end part of the Ph.D. when deadlines were approaching and tasks piling up, learning these management skills was crucial. Luckily there was a course about these topics in the last year of my Ph.D. and this saved my research project. These skills are important for the future as well.

What do you think is the biggest challenge women in evolutionary biology face? Things have gotten better for women in science, but many things persist like the glass ceiling in academia preventing women from climbing up the career ladder. Fortunately, there have been measures taken to make academia more diverse. Diversity in researchers helps us to make better science.

What did you like most about your job? Every day I learn something new, and I love how I can use my creativity in solving biological questions. I have also met so many awesome people, who have helped and inspired me. The colleagues around me have made this the best job ever.

In summary, the evolution of sex is a fascinating and complex area of study in biology. It involves the interplay of various selective pressures, trade-offs, and genetic mechanisms. While there are many theories and hypotheses, ongoing research continues to shed light on the intricacies of sexual reproduction and its evolution. In the next chapter, we will dive deeper into the genetic mechanisms involved in establishing biological sex.

Think, Pair, Share

How do you think Miriam Minken's life would have been different if she were treated equally? How might it have changed the course of IVF research?

Cell division is essential for reproduction but not for sex, explain.

Why can't biologists agree on the driver(s) of sexual reproduction?

Given the costs, is sexual reproduction worth it?

Deeper Questions

Parker defines biological sex as it relates to gamete size. Is this an adequate definition? why or why not?

If you could design the perfect experiment to test how essential sex is for evolution what would it entail?

Sexual reproduction is responsible for much of the diversity of life on the planet but not all. In what ways does diversity arise without sex?

What reasons might there be for extremophile rotifers to utilize facultative sexual reproduction rather than obligate sexual reproduction?

Key Terms

Anisogamy
  Apomixis
  Automixis
  Diploid
  Diplotonic
  Diplohaplotonic
  Gamete
  Germ cells
  Haploid
  Haplotonic
  Homologous chromosomes
  Meiosis
  Mitosis
  Muller's Ratchet Hypothesis
  Natural selection
  Oogenesis

Recombination
Red Queen Hypothesis
Sex
Sexual cascade
Somatic cells
Syngamy
Zygote

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Suggested Readings

"The Red Queen: Sex and the Evolution of Human Nature" by Matt Ridley – This book explores the role of sexual reproduction in the evolution of complex organisms, including humans. Matt Ridley discusses various aspects of sexual selection and its impact on human behavior and biology.

"Why Sex Matters: A Darwinian Look at Human Behavior" by Bobbi S. Low – Bobbi Low takes a scientific approach to examine the evolutionary basis of human sexual behavior, covering topics such as mate choice, sexual conflict, and reproductive strategies.

"The Evolution of Beauty: How Darwin's Forgotten Theory of Mate Choice Shapes the Animal World—and Us" by Richard O. Prum – This book explores Charles Darwin's theory of sexual selection and how it has influenced the development of extravagant traits and behaviors in animals, including humans.

"The Dawn of the Deed: The Prehistoric Origins of Sex" by John A. Long – Paleontologist John A. Long delves into the evolutionary history of sexual reproduction, tracing its origins in ancient aquatic organisms and its subsequent diversification.

"The Social Conquest of Earth" by Edward O. Wilson – While not exclusively about the evolution of sex, this book by renowned biologist Edward O. Wilson delves into the evolution of social behavior, which is closely tied to reproductive strategies and mate selection.

"Sperm Wars: Infidelity, Sexual Conflict, and Other Bedroom Battles" by Robin Baker – Robin Baker delves into the evolutionary biology of human sexuality, particularly the role of sperm competition and sexual conflict in shaping reproductive strategies.

Interesting Podcast

TED radio hour How birds, bees and bugs multiply and thrive

2.

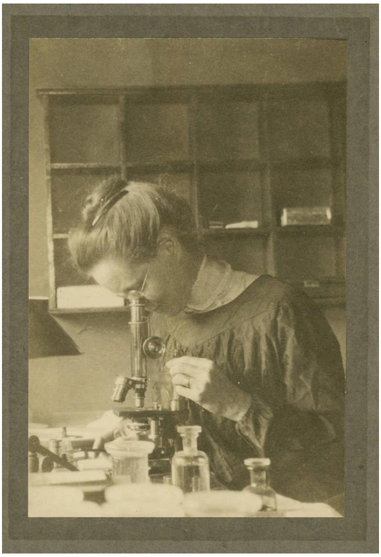
GENETICS OF SEX

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Explain the role of sex chromosomes in genetic sex determination
- Compare and contrast different modes of sex determination
- Discuss what a"master switch" is for sex determination
- Recall how the X chromosome is distinct from the Y chromosome
- Describe how ESD is different from GSD
- Contrast the dosage compensation mechanisms
- Explain the process of gonadal development
- Discuss the complex nature of sex determination
- Describe DSDs and explain how they can occur

Nettie Maria Stevens discovers sex chromosomes

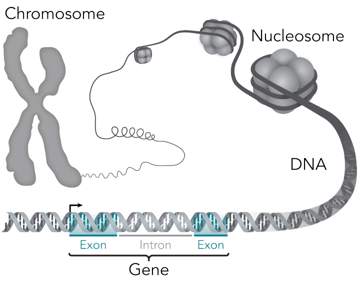


Dr. Nettie Maria Stevens in the lab, Courtesy, Bryn Mawr College Special Collections.

Nettie Maria Stevens (pictured on the right) has the distinction of being the first woman geneticist in the male-dominated world of the early 1900s. Through persistence and hard work, she discovered sex chromosomes and posited how they fit with Mendelian principles of heredity. Studying insects as a student first at Stanford and later as an Assistant Professor at Bryn Mawr, Stevens was able to determine that females have two X chromosomes, and males only one X chromosome. Stevens was also the first to identify that males had a single, small chromosome (the Y chromosome) and recognize its association with male development (Stevens 1905). She was able to complete an amazing amount of work in a short amount of time especially given that most doors were closed to women in science at that time. Thomas Hunt Morgan commented on her excellence in a letter of recommendation for her saying: "of the graduate students that I have had during the last twelve years I have had no one that was as capable and independent in research work as Miss Stevens . . ." (Brush 1978). Stevens was able to earn her Ph.D. at age 42 at Bryn Mawr, only after working long enough to save up for tuition as a teacher/librarian and proving herself through numerous research assistant positions from Stanford's Hopkins Seaside Laboratory to the University of Würzburg, working with Theodor Boveri.

Steven's death at age 50 from breast cancer tragically truncated her career. Carey et al., (2022) provide a review of her accomplishments noting that when her paper was published another male scientist (E. B. Wilson) also published his findings just months ahead of Stevens. Wilson was a good friend of Thomas Hunt Morgan's and he was aware of Nettie's research, giving her credit in the footnotes of his paper. Yet, he did not agree with her interpretation and was incorrect in his assumption that sex was determined by environmental factors in Hemipteran insects rather than by sex chromosomes. However, it was Wilson who was internationally recognized for the discovery of sex chromosomes, not Stevens. Moreover, just a year after the publications, Morgan and Wilson were invited to speak at a conference to present their research on sex chromosomes whereas Stevens was not invited (Ogilvie and Choquette 1981). Even so, historians recognize that Stevens' conclusions were more robust and Wilson did not quite understand the implications of the discovery while Stevens understood just how highly consequential they were (Brush 1978; Kingsland 2007). Her foundational research led to numerous discoveries about the genetics of sex.

A brief review of Chromosomes, DNA, and Genes



Each chromosome is made up of tightly packaged DNA. DNA is made up of nucleotides, A,T,C,G, the order within a gene determines the RNA sequence and protein sequence. A gene sequence can be on either strand of DNA.

Humans have 23 pairs of chromosomes, twenty-two of which are autosomes that do not differ between the sexes. The remaining two chromosomes, the X chromosome, and the Y chromosome, are **sex chromosomes** that differ between biological females and males (XX and XY respectively). Chromosomes are only visible during the M phase of the cell cycle (see previous chapter). They are the condensed packaging units of the DNA (deoxyribonucleic acid), a double-stranded molecule that encodes the genetic information in its sequence which is comprised of four nucleic acid monomers guanine, thymine, cytosine, and adenine (G, T, C, & A) pictured on the right. Each chromosome consists of both DNA and associated proteins. The structure of a chromosome is hierarchical and organized at multiple levels, allowing for efficient packaging and proper distribution into daughter cells during the M phase. During most of a cell's lifetime, a portion of the DNA is in a less condensed state known as chromatin which allows the cell to have access to its information. This is because within the DNA lies an organism's genes which are specific segments of DNA that contain the instructions for building proteins and RNA (ribonucleic acid) molecules. Each gene is comprised of a series of nucleotides with every three bases encoding information for a particular amino acid (protein monomer) known as a codon.

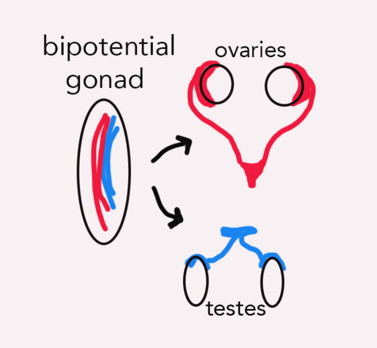
Codons serve as the basic unit of the genetic code, and they are the "words" that specify the amino acids to be incorporated into a protein during protein synthesis. There are 64 possible codons, which correspond to the 20 standard amino acids and three "stop" codons that signal the end of protein synthesis. During transcription, the gene is read and transcribed into a single-stranded messenger RNA (mRNA) molecule. The mRNA is then translated by ribosomes into a sequence of amino acids which then fold to create a functional protein. Collectively the process of transcription and translation is referred to as gene expression and it is highly regulated. The complete set of an organism's genetic material is known as its genome however only a small portion of the DNA contains protein-coding genes. When writing about genes and their respective proteins the gene name is usually in lowercase letters and italicized whereas the protein is capitalized, (e.g. sry is the gene and SRY is the protein).

In animals as diverse from one another as fruit flies are to mammals, genes play a central role in the determination of biological sex. However, the location of genes, the number of genes involved, the timing of their expression, and the influence of environmental factors differ and thus a single universal method of sex determination across all species does not exist. Sex determination mechanisms can be quite diverse and can differ even among closely related species.

How is biological sex determined?

Biological sex is not to be confused with gender, they are two different concepts. Biological sex is associated with multiple biological attributes including hormone levels, sex chromosomes, and reproductive anatomy. Gender is limited to socially constructed roles and behaviors. For more information on the relationship between biological sex and gender see the chapter on *Gender and Sexuality*.

The bipotential gonad



In the early embryo, the gonad is bipotential meaning it can differentiate into either ovaries or testes depending on which pathway is initiated, image by Jennifer Dever CC BY-NC-ND.

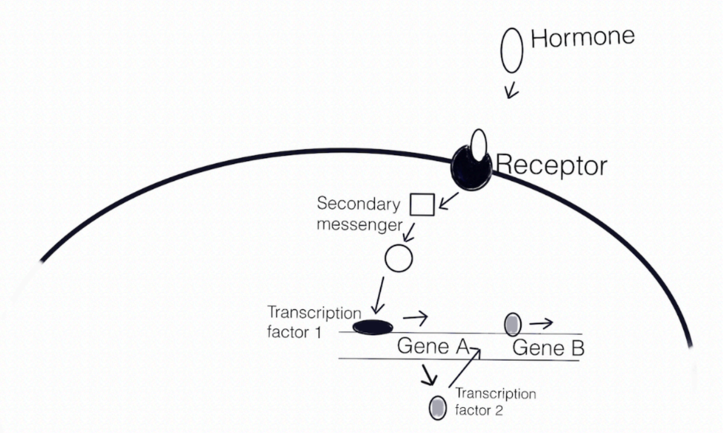
In nearly all sexually reproducing organisms, biological sex is **dimorphic** (there are only two distinct forms of sex). Individuals have the potential to produce either eggs or sperm and only on very rare occasions make both. When and how sex determination is initiated is highly variable but all animals share a common feature: the reproductive organs involved in gamete production come from primordial germ cells that are biopotential. Biopotential means that these primordial germ cells can differentiate into either female or male reproductive organs (as depicted in the image on the left). A decision is made during a critical window of time in early embryonic development to determine whether or not the reproductive organs form that produce either eggs or sperm. Sex-determining signals that are responsible for this decision have evolved independently multiple times and there is a high degree of variation across taxa as to how sex is determined (Stöck et al. 2021).

What we know about sex determination comes from mutational studies in the following model organisms: the roundworm (*Caenorhabditis elegans*), the fruit fly (*Drosophila melanogaster*), the zebrafish (*Danio rerio*), and the mouse (*Mus musculus*). Each offers important insight into the molecular mechanisms involved in the commitment to becoming female, male, or hermaphrodite. The commitment part of the process is referred to as determination and the realization of becoming phenotypically female, male, or hermaphrodite is referred to as differentiation.

Genetic Sex Determination (GSD)

A series of events unfurl after fertilization that orchestrates embryonic development. The overall body plan is determined by the expression of specific genes and the localization of gene products within the embryo. The gene products participate in regulatory pathways (shown in the diagram below) that often work together in a network. A regulatory pathway involves a series of genes being expressed (transcribed and translated) and/or repressed (blocked from being transcribed and translated).

The steps of a regulatory pathway are 1) binding of ligand (e.g. a hormone) to a receptor causes a change that 2) sets off a series of events (secondary messengers convey the signal), and 3) the signal activates transcription factors present to interact with the regulatory elements of genes and express the gene that encodes a transcription factor, 4) the new transcription factors accumulate, and together with other transcription factors, bind to different, previously inactive regulatory elements, and a yet again new state is generated. The simplified illustration below shows how a pathway results in the expression of several genes. This can also be described as a signaling cascade.



Generalized regulatory pathway. A hormone binds to the receptor causing a change that leads to a cascade of events involving secondary messengers and transcription of genes, the products of which are often transcription factors that induce the expression of additional genes, image by Jennifer Dever CC BY-NC-ND.

To initially kick off the cascade of events, GSD often involves a specific master switch gene "delicately poised to respond to the initial trigger to be male or female and then to amplify this decision" (Swain and Lovell-Badge 1999). As in the case with humans, this switch is localized on the Y chromosome which is responsible for triggering the male-specific cascade. Biological females have a pair of X chromosomes instead and therefore do not have a Y chromosome. These sex-specific chromosomes are referred to as sex chromosomes first discovered by Nettie Maria Stevens in 1905 (see previous chapter), the remaining chromosomes are called autosomes. Suppression of recombination during meiosis led to the differentiation between the sex chromosomes allowing for the evolution of GSD (Charlesworth, Charlesworth, and Marais 2005). The unifying factor in GSD is that the decision lies in the sex chromosomes. Individuals who have two of the same sex chromosomes are referred to as the homogametic sex symbolized as XX (as in female mammals), or ZZ (as in male birds) and those with two differing sex chromosomes are heterogametic as in XY (as in male mammals) or ZW (as in female birds).

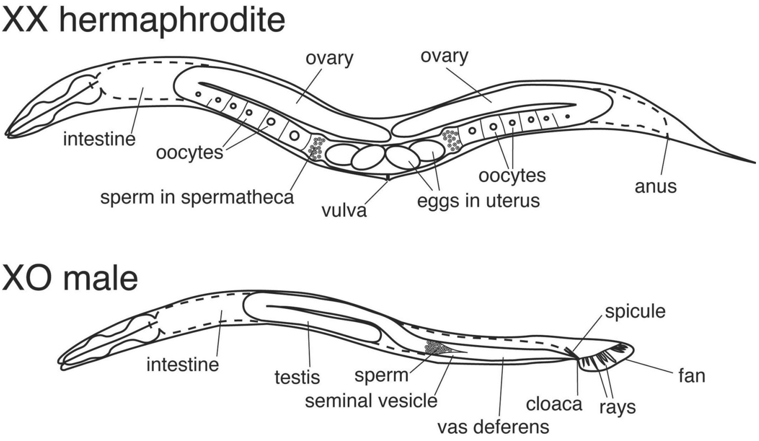
Females have two Xs and males one, how is gene imbalance dealt with?

Dosage compensation

In diploid organisms, each cell has two complete sets of chromosomes. However heterogametic individuals have two different sex chromosomes, with one chromosome in the pair significantly larger than the other as in the case of the human X and Y chromosome. This results in unbalanced gene expression because the larger X chromosome has many more genes than the smaller Y chromosome (Bridges 1925). On one hand, this difference is essential for the regulation of sex-specific genes but on the other hand gene imbalance is associated with numerous problems such as disorders and cancer. Therefore mechanisms have evolved to compensate for the imbalance, termed dosage compensation, such as increasing the level of expression of genes on the X chromosome in the heterogametic male or lowering the level of expression of genes on the X chromosome in the homogametic female.

In nematodes (*C. elegans*) it's the ratio of XSEs:ASEs

The nematode roundworm, *C. elegans*, has been a model organism in genetics for some time. They have two different "sexes": hermaphrodites that undergo both oogenesis and spermatogenesis for self-fertilization pictured below, and males that can produce only sperm to fertilize hermaphrodites via sexual reproduction. Most *C. elegans* are hermaphroditic and overall their genetic diversity is much lower than that of other obligatory sexual species in the same genus (Félix and Buhay 2010). In the wild, these small roundworms inhabit highly changing environmental conditions that can often lead to long stretches of isolation which may have led to their ability to self-fertilize (Schulenburg and Félix 2017).


XX hermaphrodite
ovary
ovary
intestine
oocytes
sperm in spermatheca
vulva
oocytes
eggs in uterus
anus
XO male
spicule
intestine
testis
sperm
seminal vesicle
fan
cloaca
rays
vas deferens

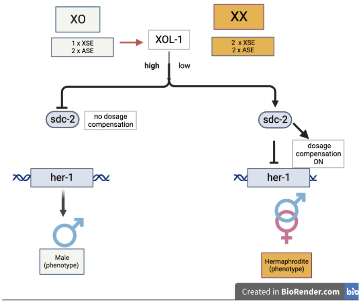
The two sexes of C. elegans. The hermaphrodites and males differ strikingly in overall body size and structures such as the somatic gonad and tail. Many other tissues and organs are sexually dimorphic, notably the nervous system and musculature. Image from *WormBook*, ed. The *C. elegans* Research Community, WormBook, doi/10.1895/wormbook.1.7.1, http://www.wormbook.org.

The XSEs and ASEs

Whether or not *C. elegans* becomes hermaphrodite or male is determined during early embryonic development through a series of interacting signals. Barbara Meyer has been investigating the coordinated mechanisms of sex determination and dosage compensation in *C. elegans* for the past 30 years and provides a thorough review of the topic (Meyer 2022). Meyer notes that it is the ratio of X chromosomes to autosomes (X:A) that is the key signal triggering the **"master switch"** that determines the cascade of events. The ability to count the number of X chromosomes and Autosomes lies with X-linked genes called X chromosome signaling elements (XSEs) and autosomal signaling elements (ASEs) respectively. These XSEs and ASEs act in opposite ways that result in different transcriptional outcomes. There are several genes involved but the **xol-1 gene** (XO-lethal) is the master switch, when it is "on" (expressed) the male pathway is chosen, when it is "off" (not expressed) the hermaphrodite pathway is chosen. The pathway is illustrated below.

C. elegans males have a single X chromosome, their genotype is XO because they lack the Y chromosome. This creates an X:A ratio of 1:2, or 0.5, therefore, the ASEs (genes sea-1 and sea-2) have a greater dosage relative to XSEs (genes sex-1 and ceh-39) and they activate the expression of the xol-1 gene. The XOl-1 protein is the master switch protein that sets off a regulatory pathway by activating the transcription of the gene her-1. HER-1 protein binds to TRA-2 receptor blocking TRA-2 activity thereby resulting in male differentiation. This also blocks dosage compensation from being induced since there is only one X chromosome in the male.

Males only have one X, (XO), the **X:A induces high expression of Xol-1**, which leads to male-specific gene expression. Hermaphrodites have two Xs (XX), and the greater X:A blocks Xol-1 resulting in female-specific gene expression and dosage compensation.


XO
1 x XSE
2 x ASE
XOL-1
XX
2 x XSE
2 x ASE
high
low
sdc-2
no dosage compensation
sdc-2
dosage compensation ON
her-1
her-1
Male (phenotype)
Hermaphrodite (phenotype)
Created in BioRender.com bio

Generalized sex determination pathway for *C. elegans*.

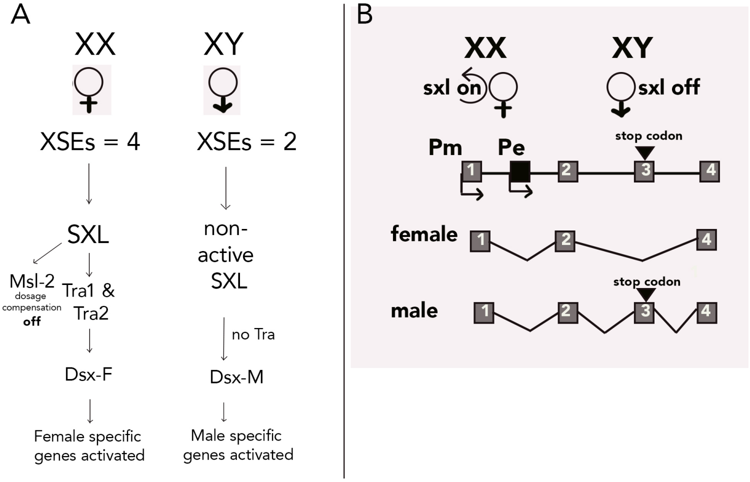
Hermaphrodite *C. elegans* results from having **two X chromosomes (XX). The X:A is 1:1, equal to one, and this initiates double expression of four XSEs:** genes sex-1, fox-1, ceh-39, and sex-2 compared to ASEs. Products of these genes block the expression of xol-1. Without active XOL-1 protein, three genes: sdc-1, sdc-2 and sdc-3 are expressed. The SDC-2 and SDC-3 proteins control dosage compensation by downregulating the expression of the genes on the X chromosomes by half. In this way, dosage compensation is attained. The sdc genes also activate the expression of tra-2 which is needed for expression of the tra-1 gene. Tra-1 proteins are responsible for hermaphrodite development and repression of male development.

In *Drosophila*, sex is determined by the number of X's

In *Drosophila* the master switch gene is located on the X chromosome is called **sex-lethal (sxl)** gene (Bell et al. 1988), and its female-specific expression is dependent upon the dosage of four additional XSEs (similar to *C. elegans*). The name sex-lethal comes from mutant analyses: improper expression in males leads to death. Erickson and Quintero (2007) provide a review of the female-specific regulatory pathway. As shown in the diagram below (A) For XX individuals, sxl is "on" resulting in female-specific functional Sxl protein. The functional Sxl protein binds to the pre-mRNA from two other genes: tra (transformer) and tra-2 which encode Tra and Tra-2 proteins. These in turn bind to the dsx (double-sex) pre-mRNA and result in the alternative splicing to make Dsx-F. The dsx gene encodes for a transcriptional regulator, the Dsx-F form that promotes female differentiation and represses male development. SXL is also involved in blocking dosage compensation by binding msl-2 (male-specific lethal) pre-mRNA and promoting splicing that results in a nonfunctional Msl-2 protein. Without the Msl-2 protein interacting with other dosage compensation genes, hypertranscription of genes on the X chromosome will not occur.

The *Drosophila* sxl gene has two promoters

To ensure the **sxl** switch stays **on in females**, the regulation of the sxl gene expression is a bit complicated. The sxl gene has two different promoters, an early female-specific promoter (**sxl-Pe**), and a maintenance promoter (**sxl-Pm**). Recall that a promoter is a regulatory sequence just upstream of the start codon in a gene that enables it to be successfully transcribed. Research by Erickson and Quintero (2007) shows that in individuals with two X chromosomes, XSEs are highly expressed in very early development. This is the key to initiating the switch that establishes femaleness. Double expression of XSEs (because there are two X chromosomes) results in the binding of the transcription complex on the sxl-Pe promoter. Illustrated in the diagram below (B), Salz and Erickson (2010) note that Sxl protein expressed from sxl-Pe causes female-specific splicing of Sxl transcripts originating from the sxl-Pm promoter which is activated at a later stage in development. This splicing prevents the inclusion of the poison exon (codon 3, which has a stop codon) in its own primary transcript. The resulting active SXL protein promotes female-specific splicing of sxl-Pm transcripts, establishing an autoregulatory feedback mechanism to keep sxl “on”. Once established, the early promoter is shut off and expression is initiated from the maintenance promoter. How this happens is not clear but the **SXL protein keeps sxl gene expression going** in each cell throughout the life of the fly (Salz and Erickson 2010).


A
XX
XY
XSEs = 4
XSEs = 2
SXL
non-active SXL
Msl-2 dosage compensation off
Tra1 & Tra2
no Tra
Dsx-F
Dsx-M
Female specific genes activated
Male specific genes activated
B
XX
XY
sxl on
sxl off
Pm
Pe
stop codon
1
2
3
4
female
male
stop codon

A) Sex determination pathway for *Drosophila*. B) Female-specific alternative splicing is controlled by transcription at early promoter PeSxl indicates Sxl transcript from the early promoter indicated by Pe. Pm indicates Sxl from the late promoter.

The male-specific pathway happens in flies with only a single X chromosome. The Y chromosome is not involved in sex determination, only fertility. The **sxl gene is not expressed** from the sxl-Pe promoter, and the **autoregulatory feedback loop is off**. Instead, transcription happens only from the sxl-Pm promoter but the transcript is spliced in a male-specific way, leaving codon 3 in the transcript, resulting in an inactive SXL (Harrison 2007). Consequently, active Tra is not produced and without active Tra, the Dsx-M form is created. Dsx-M promotes male differentiation. Also, the lack of SXL results in functional Msl-2 protein which promotes overexpression of X-linked genes for dosage compensation (since XY individuals only have a single X chromosome) (Bashaw and Baker 1995).

How is the transcription from the sxl-Pe prevented in males? Early sxl gene expression is blocked by **ssx** (Sister of Sex-lethal) gene expression whose product is a competitive inhibitor of the sxl auto-regulatory loop (Moschall et al., 2019). Without active SXL protein to bind at the sxl-Pe, only sxl-Pm is bound and this produces an mRNA that includes the male exon with the stop codon, and no active SXL is made. Compared to other insects what happens in *Drosophila* with sxl as the "master switch" is the exception rather than the rule (Evans and Cline 2013).

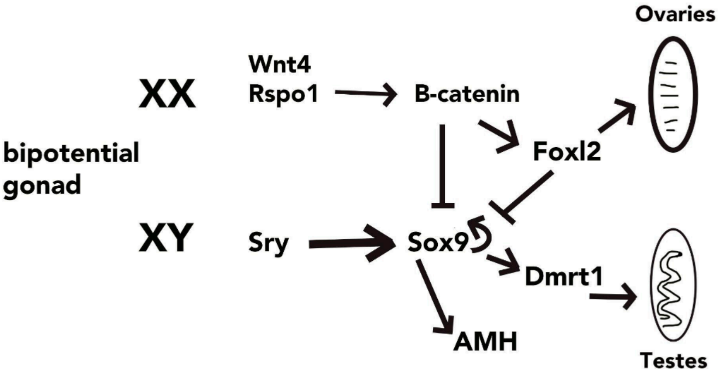
Mouse: a model for human sex determination

The mammalian sex-determination system is a **XX/XY** system. The specific details of molecular mechanisms remain poorly understood due to the complex nature of developing mammalian gonads (Stévant and Nef 2019). Unlike *C. elegans* or *Drosophila*, sex determination in mammals is not based on the ratio of XSEs to ASEs, nor the number of X chromosomes rather **it is the presence/absence of the master switch gene** that determines the fate. The Y chromosome contains the switch: the sry gene (sex determining region of the Y chromosome).

Mammals with two X chromosomes become

biologically female

What we know so far comes from extensive studies using mice illustrating that numerous factors are needed to work together in a chorus-like fashion to activate one pathway while simultaneously repressing the other. The review by Eggers, Ohnesorg, and Sinclair (2014) paints a complicated picture of mouse sex determination. During fetal development (10.5 days post-conception), determination is initiated solely in the fetal germ cells located in the genital ridges (gonadal primordia). The sry gene encodes a transcription factor known as testes determining factor (Tdf) and sry expression is activated by several transcription factors including Six1, WT1, and Gata4. The regulatory pathway is depicted in the simplified diagram below. The master gene sry, when expressed produces the protein Tdf that activates the expression of the sox9 gene. The sox9 gene also encodes a transcription factor that leads to testes development by activating the expression of numerous downstream targets involved in Sertoli cell (site for sperm cell production) and Lydig cell (site for androgen production) differentiation such as dmrt1.


Ovaries
XX
Wnt4
Rspo1
B-catenin
Foxl2
bipotential
gonad
XY
Sry
Sox9
Dmrt1
AMH
Testes

The gonad of embryos with a Y chromosome differentiate into males because the Sry gene, located on the Y is expressed. SRY induces the expression of Sox9. Sox9 activates the expression of several male-specific genes. In XX individuals, Sry is absent. Instead, female-specific genes are expressed, and the male pathway is repressed.

The mammalian female pathway

The female pathway is still not yet well understood. So far several genes involved in the regulation of ovary differentiation have been identified including wnt4, rspo1, ctnnb1, and foxl2.The wnt4 and rspo1 gene products interact to activate the expression of ctnnb1 that produces β-catenin that promotes ovarian development and represses testis-formation. It appears that a balancing act between rspo1 and sox9 is achieved (Rotgers, Jørgensen, and Yao 2018). The foxl2 gene also encodes a transcriptional regulator protein (FOXL2) that suppresses sox9 expression thereby blocking testes formation and this continues throughout adulthood. FOXL2 protein is also important for ovarian cell differentiation (Uhlenhaut and Treier 2006). The dax1 gene product has been shown to block male development but it is also needed for testes development in males therefore the timing of its expression is likely critical to the outcome. Further research is required to elucidate the complexity of the female pathway.

In female mammals, one X is permanently inactivated

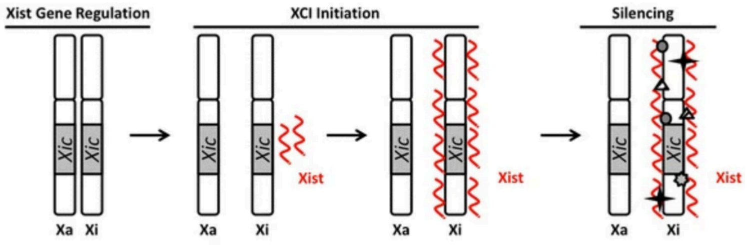
Dosage compensation in mammals involves the random shutdown of one of the two X chromosomes, known as X inactivation. Mary Lyon was the first to explain the mechanism, stating that one of the two X chromosomes in female cells is randomly shut down during early embryonic development (Lyon 1961). Moreover, she predicted that all of the daughter cells throughout the animal's life contain the same inactivated X chromosome. Lyon conducted several genetic crosses in mice supporting her hypothesis (Lyon 1962). This was ground-breaking and she was able to unify several lines of previous experimental data to solve the question of how dosage compensation occurs in mammals (Harper, 2011).

The same X inactivation mechanism occurs in all placental mammals, whereby a long noncoding RNA gene, xist (X inactive-specific transcript) found in a region of the X known as the X-inactivation center (XIC) is expressed from a single X chromosome. The resulting XIST RNA works together with chromatin remodelers to inactivate the X and maintain a silent state (Brown et al. 1992; Plath et al. 2002). Approximately 12-20% of genes located on the X chromosome escape inactivation in humans depending on which tissues they are in, and these genes remain accessible to transcription because they contribute to female-specific differences (Tukiainen et al. 2017). According to Zito et al. (2023) the "genes that escape inactivation have both heritable and environmental components...with genome-wide effects and mutations that impact the escape have complex phenotypical consequences."

How does XIST work to inactivate an X?

Xist RNA provides a structure for the assembly of other epigenetic factors, changes are modifications to DNA that regulate whether genes are turned on or off, making the Xist RNA essential for X inactivation (Lu et al. 2016). The precise mechanism is still being determined but according to the review by Brockdorff and Turner, (2015) xist is transcribed from one chromosome (Xi), the **Xist RNA spreads** over and covers the selected chromosome, recruits other proteins that encourage histone modifications and DNA methylation thereby promoting condensation of the chromosome into a **Barr body**. An antisense **Xist transcript is transcribed from the tsix** gene on the remaining X chromosome (Xa) to **block xist** from being expressed or binding to the **Xa which remains active** (illustrated below). When the cell divides the Barr body is replicated and remains compacted.

The number of X chromosomes in the cell is counted so that **only one will remain active**. Evidence suggests that autosomal factors stimulate Tsix expression with a competition between Xist repression and activation and the choice is usually random but may be biased for heterozygous alleles. The phenomenon known as skewed X inactivation occurs when "more than 75% of cells in an individual choose the X chromosome from one parent as the Xi" (Sun et al., 2022). A recent study by Dou et al., 2024 suggests in damaged cells Xist RNA and associated proteins act as antigens stimulating autoimmune attack which may be the reason females experience such a high incidence of autoimmune disease compared to males.



The number of Xs is counted. One is randomly chosen, and the other(s) undergo inactivation (Xi). Xist is expressed, and its RNA transcript binds to the XIC of the chromosome that will be inactivated (Xi). Tsix transcript blocks the inactivation of the other chromosome (Xa).

Mammals with XY chromosomes become biologically male

To block the female developmental pathway illustrated above, **Sox9 activates the amh gene** (Anti-Mullerian Hormone, also known as MIS) which causes the regression of the female ducts, and Sox9 is needed for the repression of female-specific genes. Maintenance of the male pathway is assured by continued expression of sox9 (it autoregulates itself) and dmrt1 which both act to keep up testicular development and block the female pathway.

The human X and Y chromosomes

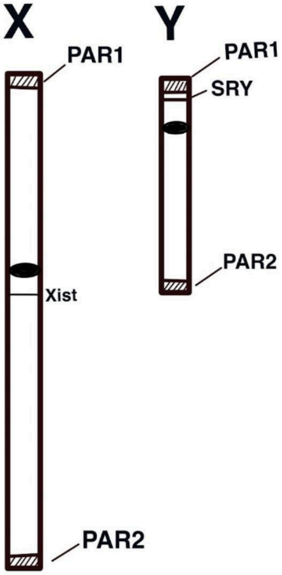


Diagram of human X chromosome (left), Y chromosome (right). PARs (psuedoautosomal regions) allow for proper pairing during meiosis. The sry gene is located on the Y but not the X, Xist gene is located on the X chromosome.

Between 180 to 210 million years ago, the mammalian X and Y chromosomes evolved from autosomes in the placental mammal lineage (Lahn and Page 1999). Recombination is an important feature of prophase I of meiosis yet for most of its length the recombination is suppressed on the Y chromosome. The resulting non-recombining male-specific region (MSY) remains differentiated from the X and is home not only to the sry gene but also to several other genes needed for male fertility. This lack of recombination has allowed the Y chromosome to stay distinct from the X chromosome but it has also led to its degradation (Charlesworth and Charlesworth, 2000). Compared to other chromosomes in the genome, the Y chromosome experiences significantly high rates of mutation from DNA replication error because the male germ line undergoes a greater number of cell divisions than the female germ line (Makova and Li 2002). So the genes located on the X chromosome evolve more slowly in comparison to those located on the Y (Kvikstad and Makova 2013). Until recently, much of the Y chromosome had yet to be sequenced due to its repetitive nature. However, an effort led by the Makova lab at Penn State and Phillippy at the Human Genome Research Institute, successfully filled in the gaps (Rhie et al., 2023). The Y chromosome encodes 66 protein-coding genes, and several genes have a male-specific role.

Both X and Y chromosomes have two pseudoautosomal regions (PAR1 and PAR2) near the telomeres (tips) which are short homologous regions that allow for proper alignment and recombination during meiosis, illustrated on right. The PAR1 region has over 29 genes that do not play sex-specific roles and do not experience the X chromosomal inactivation described above (Colaco and Modi 2018). A third region of homology, the X-transposed region (XTR) is evidently the result of a duplication event following the human-chimp divergence (Ross et al. 2005).

By comparison, the X chromosome has over 150 Mb DNA sequences, over half of which are repetitive. Although the chromosome has significantly fewer genes than most autosomes it still has appreciably more than the Y chromosome, encoding over 1,400 genes (NCBI, 2023).

Why is it called the X chromosome?
McKusick (1962) points out that in 1891 while examining chromosomes from the European firebug in mitosis, Henking found a "peculiar chromatin- element and was uncertain of its nature so he labeled it "X". Thus, the X chromosome…owes its name to the obscurity of its nature at first discovery."

Q&A with Dr. Kateryna Makova, PhD

Professor of Biology, Verne M. Willaman Chair of Life Sciences, Penn State University

Dr. Kateryna Makova, PhD.

Why do you study molecular evolution? specifically, what drew you to the sex chromosomes and the role of the Y chromosome in evolution? I have always been fascinated by DNA and molecular biology, but I became specifically interested in molecular evolution during my PhD. studies. As a postdoc at the University of Chicago, one of my projects was on male mutation bias – a higher number of mutations originating in the male versus the female germline. I worked with a fragment of DNA that was present on both the Y chromosome and chromosome 3, and I found that it mutates much faster on chromosome Y. It was also much more difficult to study this fragment on the Y chromosome because of its fast evolution (many of the primers I was designing were not working!), so I was wondering what the structure of the Y chromosome is. This was in the early 2000s. I had no idea it would end up being so complex when we deciphered the complete sequence of the human Y in 2023!

What do you enjoy most about your research? The thrill of discovery! I still get that feeling of excitement when I have learned something that nobody had known before and we I will be able to share it with others. I honestly have an adrenaline rush and goosebumps during these moments. They keep me going! The ability to share these moments with my students and postdocs has been and is still extremely rewarding.

What do you find most challenging about your career? Time. There are only 24 hours in a day! There are so many things I would like to investigate, but I cannot investigate them all. Therefore time management is very important and I must prioritize. I have certainly become much better at this after I became a parent.

What advice do you have for current and future women scientists? Be persistent and never give up. It is also important to make sure that you celebrate every success, even a very small one. And remember to enjoy it. As my PhD. advisor taught me, to do science only if one really likes it. If you find yourself not enjoying what you do most of the time – do something else. Life is too short!

Polygenic GSD in the zebrafish

Lateral views of adult male (top) and female (bottom) zebrafish.

The XX/XY systems are governed by a single master switch that determines sex. It is important to recognize that not all animals have a "master switch" to determine sex, and sex is not static for all adult animals. In a **polygenic** system, there is no single "master switch" instead **multiple loci found on different chromosomes work together** to contribute to sex determination as depicted in the diagram to the right (Kosswig 1964). Zebrafish have been studied for over 50 years and yet the details regarding sex determination for this species are still unclear. Wild-caught zebrafish have ZZ/ZW sex chromosomes but they do not differ in size or significant DNA content (Bradley et al. 2011). Genomic investigations suggest the presence of a sex-specific region on chromosome 4 (Anderson et al. 2012) yet several other genes implicated in sex determination are distributed throughout the genome (Orban, Sreenivasan, and Olsson 2009; Liew et al. 2012) and experimental crosses support multiple loci being involved as in a polygenic system.

The following autosomal genes have been identified by Kossack and Draper (2019) as playing an important role in zebrafish sex determination each having orthologous (similar because they are shared through common ancestry) to mammalian sex-determining genes. The dmrt1 gene is involved in male development, similar to mouse Dmrt1. Mutants develop into female fish. Another important orthologue amh (Amh in mammals) is expressed in both male and female zebrafish. In males, it represses female duct development, and in females, it is expressed in the cells of the ovary. Additionally, the orthologue to mammalian Dax1 (NROB1), nr0b1, encodes a gene product that plays a role in the expression of cyp19a1a, a female-specific aromatase-encoding gene. Aromatase is involved in the conversion of androgen to estrogen, a key hormone involved in female-specific gene expression. Two duplicated orthologues of Wnt4 are present in the zebrafish genome and wmt4a mutants are unable to develop functional reproductive ducts. Duplicated Foxl2 orthologues have also been found in the zebrafish genome, foxl2a and foxl2b. These are implicated in maintaining female differentiated fate.

How each of these genes is regulated has yet to be determined and to make the situation more complicated, lab-raised zebrafish do not adhere to a strict GSD mechanism. They lack apparent sex chromosomes (Sola and Gornung 2001). Sex ratios depart from the expected 1:1, female:male in domesticated lines. There is evidence that suggests under certain conditions zebrafish sex determination may be sensitive to environmental influences as well (Abozaid, Wessels, and Hörstgen-Schwark 2012).

Q&A with Dr. Michelle Kossack, PhD.

Postdoctoral Researcher in the Plavicki Laboratory at Brown University

Dr. Michelle Kossack, PhD.

What drew you to studying zebrafish, and specifically sex determination and reproductive biology? I had always loved the ocean, I taught marine science and SCUBA diving as a teenager. After seeing plastic pollution in the ocean and learning about estrogenic plastics I became interested in understanding how plastics could disrupt sex hormone signaling in our environment. My dissertation research in the mechanisms of sex determination in zebrafish was a natural combination of all of my previous passions. Because zebrafish are a common model for human health, and the genetic forces of sex determination were still unknown, this project not only provided a foundation for understanding environmental endocrine disruption but also could inform human reproductive biology.

What have you enjoyed most about your research? That is such a hard question! I think to be able to sustain a career in research you have to enjoy many different parts of it. I love working with fish and using their unique biology to understand human health. I love analyzing data to answer my hypothesis, and I love communicating findings in my writing and public presentations.

What do you find most challenging about your career? One of my weaknesses is patience. I constantly want to know more, and I want to know it now! But, if you have ever worked in research, you know research does not care about your timetable; it moves slowly and methodically and never works the first time around. I find it challenging to slow down and appreciate each small thing, especially when those things aren't working in your favor.

What advice do you have for current and future women scientists? Define your own success. As you build your career two things will be true: one, there will always be more you can or could do, and two, others will always appear to be achieving more than you. You have to define what you want and work to achieve what you want because it is what you want. In the pursuit of your goal, celebrate early and often! Each step towards your goal is worth a celebration. Some days your celebration will be for an experiment finally working, and some days you will celebrate getting a paper accepted. Each is worth congratulating yourself on taking a step towards your goal.

Environmental Sex Determination

Saltwater crocodile's sex determined by the temperature of the nest where the eggs undergo incubation. Photo taken by Dever.

In environmental sex determination (**ESD**) the key signal(s) that sets off the events culminating in becoming female or male is/are environmental cues to which the developing embryo is exposed during a critical time (Bull 1980). ESD has been observed in all crocodilian species, most turtle species, tuatara, many lizard species, and some fish whereby ambient temperature during incubation is the determining factor (Bull 1983; Mitchell et al. 2006). In crocodilians, research suggests a critical window exists during embryonic development which is sensitive to a narrow temperature range. with most species exhibiting an FMF pattern whereby "low and high temperatures produce a predominance of females, and intermediate temperatures produce mainly males" (González et al., 2019). Although this appears to be quite different from GSD, data indicates a similar underlying mechanism exists involving both commitment to one developmental fate and suppression of the other (Lin et al., 2018).

Why might ESD have evolved?

Phylogenetic studies support the hypothesis that ESD is the ancestral state of sex determination in reptiles, however, it appears to have evolved independently multiple times (Janzen and Paukstis, 1991). Bull (1983) suggests that if environmental conditions are more beneficial to a particular sex, ESD will be favored over GSD because it could produce skewed sex ratios. As in the case with GSD organisms, the reptilian gonad has bipotential primordium that can differentiate into either female or male reproductive organs. The specific molecular mechanisms that occur during determination and differentiation are yet to be discovered but orthologous genes have been found in ESD reptiles that are expressed during embryonic development in a sex-specific manner such as Dax1, Dmrt1, Foxl2, Sox9, and Wt1 (reviewed in (Rhen and Schroeder 2010).

The decision of which path a bipotential gonad will take is important and involves a variety of mechanisms. In the vast majority of organisms, sex chromosomes are where sex-specific genes reside and determine the development of female or male traits.

Those lacking specific sex chromosomes use a polygenic mechanism, environmental sex determination, or a combination to establish the pathway. In all cases, downstream orthologous genes point to a shared ancestry with conserved pathway participants.

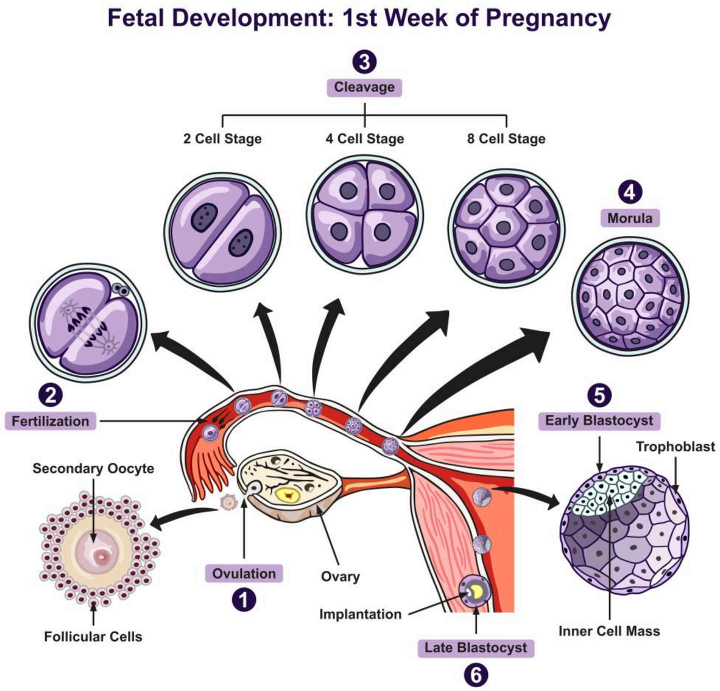
Sequential hermaphroditism

For several species of teleost fish, sex is not a fixed fate. Adult individuals change from one sex to another in a process called sequential hermaphroditism (Frisch 2004). These fish can respond to signals often related to body size that stimulate major gonadal and behavioral changes during their reproductive cycle (Wu, Dufour, and Chang 2021). This provides a level of flexibility lacking in those with fixed separate sexes (also known as gonochorism) and may have evolved under situations where the reproductive value of functioning as the opposite sex exceeds that of the current sex. This is known as the sex allocation theory (Warner 1988). Two modes of sequential hermaphroditism have been identified across several different families: (1) protogynous (female-to-male) and (2) protandrous (male-to-female) (Warner 1975). It is yet unclear how sex change in fish is facilitated at the genetic level but as Todd et al. (2016) point out, "sexual fate depends not only on activating one or other sex-specific set of genes but on continued suppression of the opposing network to maintain that fate throughout life…so the sex change likely involves a "manipulation by factors that interrupt supremacy of the prevailing sexual network and allow a takeover by that of the opposite sex."

Embryonic development of the reproductive system

In mammals, the female reproductive system begins differentiation during early embryonic development. By studying mouse embryo models researchers have been able to deduce the physical changes happening during human embryonic development. A pioneer of mouse embryology was Dr. Ann McLaren (pictured on left) who passed away in 2007. After completing her doctorate at Oxford in 1952, McLaren started studying the role the maternal environment (uterus) plays in embryonic development and she became the first to successfully grow mouse embryos in vitro and subsequently implant embryos into female mice, creating chimeras (McLaren 1976). A chimera contains multiple genetically distinct cell lineages within the same organism. This allowed her to investigate germline mutations and study gene function in the early-developing mouse. McLaren was able to use chimeras to ask key questions about sex determination and germ cell differentiation, furthering an understanding of pluripotent stem cells. A pluripotent stem cell is a type of undifferentiated cell in an early embryo with the remarkable ability to differentiate into various cell types within the body. McLaren published 300 papers and was the first woman to hold office in the Royal Society, she was presented with the title Dame Commander of the British Empire in 1993. Tam and Lovell-Badge (2007) described McLaren's groundbreaking work as “outstanding” and stated how she had a “positive and enduring influence across many topics in biology.”

Overall, McLaren had a huge impact on our understanding of embryonic differentiation. Differentiation and fetal development in utero is a complex process involving several genes, embryonic cell positioning and communication, and the maternal uterine environment. Below is a general overview of differentiation post-fertilization of the transformation of the zygote from an embryo to a fetus (see illustration below).


Fetal Development: 1st Week of Pregnancy
3
Cleavage
2 Cell Stage
4 Cell Stage
8 Cell Stage
4
Morula
2
Fertilization
5
Early Blastocyst
Trophoblast
Secondary Oocyte
Ovulation
1
Ovary
Implantation
Follicular Cells
Inner Cell Mass
Late Blastocyst
6

Depiction of cleavage stages going from a single-cell zygote to a multi-cell blastocyst with an inner cell mass and outer trophectoderm.

Embryonic development terms

Cleavage: A series of mitotic divisions whereby the volume of egg cytoplasm is divided into numerous smaller nucleated cells called blastomeres.

Morula formation: The cells of the compacted embryo divide and produce a 16-cell small group of internal cells surrounded by a larger group of external cells.

Blastocyst formation: 64-cell stage characterized by an outer layer (trophoplast) and inner cell mass (ICM); the trophoblast gives rise to the placenta and the ICM gives rise to the fetus. The ICM cells are pluripotent stem cells.

Implantation: ~6-7 days post conception (d.p.c.) having traveled down the fallopian tube the blastocyst reaches the uterus and then attaches implants into the uterine lining.

Gastrulation: The cells of the blastula are rearranged into the three germ layers: ectoderm (outer layer), endoderm (inner layer), and mesoderm (interstitial layer).

Germ layer differentiation: Each germ layer gives rise to different tissues and organs in the body; the ectoderm develops into structures such as the nervous system skin and hair, mesoderm gives rise to the muscle-skeletal system circulatory system and reproductive organs, and the endoderm forms the lining of various internal organs.

Organogenesis: Once the three germ layers are established organogenesis begins during this phase the cells within each germ layer undergo further differentiation and specialization to form specific tissues and organs.

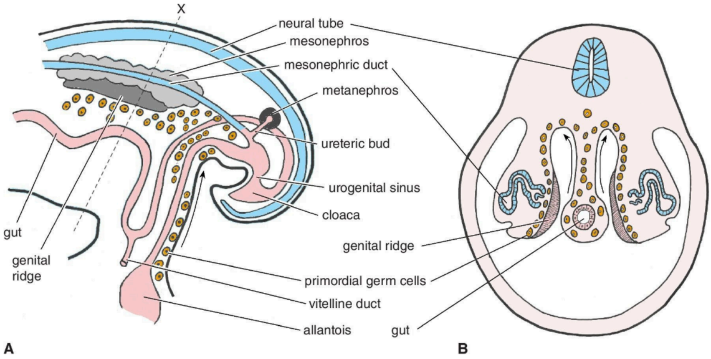
Fetal development: As differentiation and organogenesis progress the embryo transitions into a fetus. At this stage, the major organs and systems are formed and throughout the remaining gestational period, the fetus undergoes further growth refinement, and maturation.

Human Embryonic Development Overview

The Bipotential Gonad

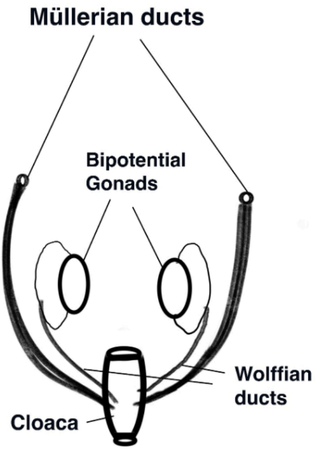
In mammals, sex determination begins with the expression of genes on the sex chromosomes (discussed above) leading to differentiation in the gonads. Expression of genes leads to sex steroid hormone production in the gonads that triggers appropriate differentiation of the ducts, glands, and associated genitalia and the decision must be maintained throughout life. The gonad forms within the developing urogenital system from the mesoderm. In the early embryo, all organs normally differentiate into only one type of organ. However, the gonads are exceptional in that regard because they are bipotential (having the ability to differentiate into either an ovary or testes) (for review see Brennan and Capel 2004).

Before the regulatory pathway of determination is triggered to become ovary or testes the embryo is in an indifferent stage that is characterized by rudimentary gonadal ridges formed from primordial germ cells (precursors to eggs and sperm). The genital ridges can be recognized by week 4 of gestation. These gonadal ridges are bilateral, ridge-like protrusions that appear ventromedially to the nephrogenic cord (a transient structure that forms during the early stages of kidney development). During this indifference stage, the epithelium of the genital ridge proliferates into the loose connective mesenchymal tissue above it. Separate from the gonads themselves, a subset of cells in the early embryo is induced to become primordial germ cells. Primordial germ cells migrate to the genital ridge (illustrated below) and become enclosed by supporting cell progeny. These germ cells undergo several successive rounds of mitosis to establish the germ cell pool.


X
neural tube
mesonephros
mesonephric duct
metanephros
ureteric bud
urogenital sinus
cloaca
gut
genital ridge
genital ridge
primordial germ cells
vitelline duct
allantois
gut
A
B

A. Route of migration of primordial germ cells from the allantois to the genital ridge, their site of differentiation. B. Transverse section through an embryo at the level indicated showing the migratory pathway of primordial germ cells along the dorsal mesentery to the genital ridge (arrows).

Formation of sex cords



By week 7 the embryo has bipotential gonads and both types of ducts that can differentiate into either female or male reproductive structures.

Once the gonadal primordium has been established the gonad is "poised to embark on the journey toward either a testis or an ovary" (Rotgers, Jørgensen, and Yao 2018). The epithelial layers of the genital ridges form the primary sex cords which will surround the primordial germ cells that migrate into the human gonad during week 6. By 7 weeks two sets of internal ducts are present: Müllerian and Wolffian (shown on the diagram to the right). Müllerian ducts are comprised of a meso-epithelial tube surrounded by mesenchyme with an outer layer of epithelium that will differentiate into the female Fallopian tubes (oviduct), uterus, and upper vagina. A comparison of vertebrate taxa from sharks to primates reveals that the initial stages of differentiation of the Müllerian ducts are a highly conserved pathway (Major et al. 2022).

Ovarian and Müllerian differentiation

In the XX fetus at approximately week 8 the sex cords regress and are replaced by a new set of sex cords that remain near the outer surface cortex of the organ (**cortical sex cords**). The cortical sex cords are divided into clusters called rete ovarii that each surround a germ cell that becomes the ova. The surrounding epithelial sex cords will differentiate into the granulosa cells and the mesenchyme cells of the ovary differentiate into the thecal cells. Granulosa and thecal cells form the follicles that develop into germ cells and secrete steroid hormones. The Müllerian duct remains intact and it differentiates into the paired epithelial tubes (oviducts), uterus, cervix, and upper vagina. The **Wolffian ducts degenerate**.

External embryonic genitalia

The external genitalia develops in the female as follows: at 8 weeks gestation a genital tubercle, the genital folds, urethral folds, and a urogenital opening are visible. The genital tubercle gives rise to the clitoris and the urethral groove persists as the vestibule. The unfused urethral folds become the labia minora, and the unfused labioscrotal folds become the labia majora.

Male differentiation

In the XY fetus proliferation of the sex cords continues, extending deep into the connective tissue (medullary sex cords). They form a network of internal medullary testis cords and rete testis cords. Apoptosis, or controlled cell death, of the Wolffian ducts is blocked. Instead, the development of the epididymis, vas deferens, seminal vesicle, and efferent ducts from the Wolffian ducts occurs. The internal cord cells become Leydig cells that make testosterone and Sertoli cells which mature into sperm. Testosterone levels gradually increase as testicular development progresses. A**ntimüllerian hormone (AMH) is produced by the Sertoli cells**, causing the Müllerian duct to atrophy.

The role of sex hormones in embryonic development

Sex determination is made when the genetic switch activates the transcription of downstream target genes. These targets result in the production of steroid hormones: estrogen and testosterone that in turn cue morphogenesis of the ovary or testes. The steroidogenic theca cell and Leyding cell lineages produce these hormones that contribute sexual dimorphism of the embryo. The steroidogenic biochemical pathway (known as steroidogenesis) is complex and involves several types of enzymes to convert cholesterol to steroids. According to a review by Bondesson et al. (2015), two important types of enzymes involved in the pathways are **cytochrome P450**

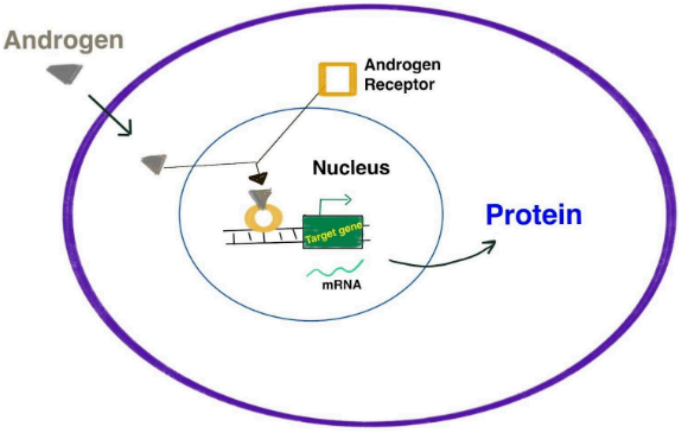
(CYPs) and **hydroxysteroid dehydrogenase** (HSDs). The two classes of sex steroids are estrogens and androgens.

Estrogens

There are three main types of estrogens formed via steroidogenesis: **Estrone (E1), 17β-estradiol (E2), and estriol (E3).** Cholesterol is converted into androstenedione and then either E1 or E2 is formed. E3 is produced through the conversion of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) originating from the fetal and maternal adrenal glands. Notably, the placenta keeps high estrogen levels from maternal placental production separate from the embryo.

Estrogens diffuse through membranes and bind to specific nuclear receptors: estrogen receptor alpha ERα and estrogen receptor beta ERβ. When bound to the ER, estrogen-ER moves into the nucleus and binds estrogen response elements on genes to activate transcription. Gene expression microarray analyses of rat XX embryos exposed to synthetic estrogen showed how estrogen was directly involved in the expression of genes involved in tissue remodeling, cell growth differentiation, and apoptosis in the ovary and uterus. Estrogen is produced in XY mammals from circulating androgens (conversion of androstenedione and testosterone) and is required to develop testes (Rochira and Carani 2023).

Androgens



Androgen binds a specific receptor to induce the expression of target genes.

Development of the testes and male duct system derived from the Wollfian ducts requires the action of androgens. Once the testicular cords have been formed **Leydig cells** start producing androstenedione (~8 weeks), which is converted into testosterone by **Sertoli cells**. Peak embryonic androgen production is reached around weeks 12-14. Fetal testosterone orchestrates male reproductive development. Similar to estrogens, androgens bind to androgen receptor (AR) and activate the transcription of genes (see image above). Bramble et al. (2016) exposed XY mouse embryos to testosterone resulting in gene expression arrays confirming testosterone-induced genes involved in male masculization. The XX fetus is also exposed to low androgen levels produced as a byproduct of corticosteroid production and from maternal adrenal glands (Gitau et al. 2005). These levels are low enough to permit the external genitalia to remain feminine.

Atypical gonadal development

What we know about sex determination and differentiation in humans comes from atypical gonadal development. There is some disagreement on how these atypical instances should be classified (González and Ludwikowski 2016). Traditionally they have been labeled as intersex conditions because the result is often ambiguous genitalia due to a combination of characteristics (eg. XX individual with internal testes). There is a lack of consensus on how intersex should be defined and no simple cause for intersex exists (Davis 2015). More recently the medical community has adopted the classification of disorders of sex development (DSDs) over the term intersex. However, the term "disorder" is also problematic because it pathologizes a person's condition and has led to misconceptions. There may or may not be a need for someone to seek treatment but the term disorder leads one to think medical corrections should be sought. A more useful way of looking at atypical development would be to take Kessler's (1998) point of view and think in terms of gonadal variability rather than ambiguity. From a patient advocacy mindset, Davis (2015) reports there is utility in embracing both intersex and

DSD, the intersex term can be empowering but the DSD term seems more practical in working with family members and the medical community. Herein we will use the term DSD but it is very important to be mindful and foster understanding, respect, and inclusivity whenever discussing atypical development.

Congenital Adrenal Hyperplasia (CAH)

DSDs are rare, occurring in approximately one in 2000–4500 births (Hughes 2008). The most common **46,XX DSD** is **Congenital Adrenal Hyperplasia (CAH),** (reviewed by El-Maouche, Arlt, and Merke 2017). CAH is due to autosomal recessive mutation(s) in gene(s) involved with enzyme production. This leads to issues in steroidogenesis and can impact glucocorticoid, mineralocorticoid, and sex steroid production. The vast majority involve 21-hydroxylase deficiency (>95%) due to a mutation in the CYP21A2 gene. This can lead to excessive fetal adrenal androgen exposure which results in virilization (development of male characteristics) of external genitalia of 46,XX. However the degree of exposure can vary and patients with non-classic congenital adrenal hyperplasia who are identified by family genetic studies, but asymptomatic are said to have cryptic congenital adrenal hyperplasia.

In **46,XY DSD** mutations in DAX-1 have been associated with X-linked **adrenal hypoplasia congenita (AHC)** which also impacts steroidogenesis, causing an underdevelopment of the adrenal gland leading to impaired pubertal development and male infertility. In very rare cases AHC can occur in girls due to "skewed X-inactivation" (Suntharalingham et al. 2015).

Androgen insensitivity syndrome (AIS)

Hormones must bind receptors and interact with other molecules to be effective. Mutations in androgen receptor (AR) genes are also associated with DSD, known as androgen insensitivity syndrome (AIS) reviewed by Mongan et al.(2015). The phenotypic effects are dependent on the level of receptor impact and is divided into three categories: complete, partial, and mild form. Complete AIS individuals are 46,XY "with testes which produce age-appropriate androgen levels but have under-masculinized external genitalia due to defects in androgen action" (Mongan et al. 2015). In the partial AIS syndrome, the degree of sexual ambiguity ranges from severe where an XY individual presents with female-like external genitalia to mild with male-appearing genitalia with infertility. Over 400 mutations in AR have been reported thus far.

Mutations in sex-determining pathway genes

Mutations in numerous sex-determining pathway genes have been identified that can lead to partial masculinization of the gonad. For example, 46,XX ovotesticular DSD is a rare subset of DSD characterized by the presence of both testicular and ovarian tissue in the same individual. Mutations in sox3 locus which can induce sox9 lead to testicular development in 46,XX. Additionally, mutations in rspo1, wnt4, and foxl2 also have been identified (Bashamboo and McElreavey 2015). External genitalia exhibit differences in infancy, "however, there are multiple cases of affected individuals who present later in life, as phenotypical males or females" (Kilberg et al. 2019). Mutations in the Y-linked testis-determining gene SRY are responsible for ~15% of XY DSD, and result in partial atypical gonadal development (Xu et al. 2020).

Sex chromosome aneuploidies

Aneuploidy is when there is an abnormal number of chromosomes. Sex chromosome aneuploidies (SCAs), having more than XX or XY may also lead to DSD. Jacobs and Strong (1959) were the first to look at a chromosome spread (known as a karyotype) of an individual who had been diagnosed as having Klinefelter syndrome. This is a diagnosis that was given to males with "small testes and poor facial hair growth" and they found that this individual had an extra X chromosome making them XXY. The common symptom of XXY is infertility and some exhibit cognitive issues due to androgen deficiency. Although there is an increased risk of breast cancer, mediastinal germ cell tumors, and osteoporosis most men live normal lives (Sokol 2012).

Jacobs et al. (1960) describe a XXX individual which they refer to as a "super female". It turns out that this label is a misnomer since females with an extra X chromosome do not exhibit any apparently unique phenotypic characteristics compared to XX individuals (Hall, Hunt, and Hassold 2006). The impact of extra X chromosomes is likely mitigated thanks to the process of X inactivation.

45,X, Turner syndrome has been associated with short stature, delayed puberty, and infertility. However, those who are mosaic for 45,X exhibit a greater likelihood of menstruation and pregnancy (Zhong and Layman 2012). Turner syndrome mosaicism is a condition that occurs when an individual has a mixture of cells with a normal chromosomal makeup (46,XX or 46,XY) and cells with a single X chromosome (45,X). This is related to the X inactivation pattern of mosaicism that can occur.

Think, Pair, Share

X and Y chromosomes are different in size, the number of genes found on each chromosome, what might be the reasons for this?

Female sex determination in mammals used to be referred to as the “default” pathway. What was the justification for this terminology and is it correct?

In *Drosophila* dosage compensation involves overexpression of genes on the X in males, but in placental mammals, it is the random inactivation of an X. Why might the mammalian mechanism have been selected?

What role do the sex hormones play in female development?

Deeper Questions

Chromosomal differentiation is key to the evolution of GSD mechanisms, explain how the X and Y chromosomes evolved.

Compare and contrast sex determination mechanisms in Drosophila and C. elegans.

Briefly explain the mammalian female and male determining pathways.

Under what conditions would ESD be selected and what evidence is there that ESD may be ancestral to GSD?

Why might there be redundancies in the developmental pathways for sex?

Why is there disagreement about the term “intersex” vs disorder in describing atypical development?

Key Terms

AIS
    Androgen
    Androgen receptor
    Aneuploidy
    Aromatase
    Autosome
    Autosomal signaling elements
    Bipotential gonad
    CAH
    Determination
    Differentiation
    Dosage compensation

DSD

ESD

Estrogens

Genital ridge

Genital tubercle

GSD

Heterogametic

Hermaphrodite

Homogametic

Intersex

Lydig cells

Master switch

Mullerian duct

Primordial germ cell

Promoter

Orthologous

Sertoli cells

Sex cords

Sex chromosome

Testosterone

Transcription factor

Virilization

Wollfian duct

X chromosome signaling elements

X inactivation

X inactivation center

Xist

XO
XXX
XXY

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Suggested Readings

"The Biology of Sex" by Anne Fausto-Sterling – Anne Fausto-Sterling provides a comprehensive overview of the biology and genetics of sex, exploring topics such as sex determination, sexual development, and intersexuality.

"The Evolution of Sex Determination" by Leo W. Beukeboom and Nicolas Perrin – This book delves into the evolution of sex determination mechanisms across different species. It covers a wide range of organisms and examines the genetic and ecological factors influencing the diversity of sex determination systems.

"Sex Itself: The Search for Male and Female in the Human Genome" by Sarah S. Richardson -This book delves into the complexities of sex determination in humans, examining the role of genetics, biology, and culture in shaping our understanding of male and female.

"Temperature-Dependent Sex Determination in Vertebrates" Nicole Valenzuela, Valentine A. Lance (Editors) – This book is a collection of essays that shows how the sex of reptiles and many fish is determined not by the chromosomes they inherit but by the temperature at which incubation takes place.

Interesting Podcasts

From Radiolab: Gonads

3.

FEMALE REPRODUCTIVE SYSTEM

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to

- Recall the difference between oviparity and viviparity
- Explain why the amniotic egg confers the ability to adopt a terrestrial lifestyle
- Discuss why internal fertilization would lead to the evolution of the sex organs
- Identify and describe the human female sex organs and external genitalia
- Discuss why comparatively little is known about female genitalia

Primary sexual dimorphism is the result of the evolution of life on land

As explained in the earlier chapter the *Evolution of Sex*, sexual reproduction involves "mating" between two different individuals and the joining of their respective haploid gametes, resulting in a genetically distinct diploid zygote. The evolution of dimorphic structures to produce and deliver gametes for successful fertilization was an important part of the trajectory of the advancement of sexual reproduction. The evolution of sex happened multiple times but also always in an aquatic environment permitting individuals to release gametes for external fertilization. As life evolved to transition to terrestrial environments, selection for modifications in the reproductive organs to support internal fertilization and protection of the developing zygote also occurred. The key features of the basic female reproductive system are ovaries that produce eggs, and accessory organs for the transfer and reception of eggs and sperm all of which are under hormonal regulation.

Internal fertilization and the amniotic egg

There is diversity in how mating occurs across vertebrate taxa. In aquatic environments, females and males can synchronize the release of gametes directly into the water, and fertilization happens externally. Species that have adapted to a completely terrestrial lifestyle are unable to engage in external fertilization because of the problem of desiccation and instead rely on internal fertilization. Males introduce sperm into the female reproductive tract whereby a sperm can fuse with an egg in a protected environment.

Oviparous
Viviparous

Comparison of oviparous corn snake on left and viviparous water snake on right.

The evolution of the amniotic egg protected by a calcified shell that houses the amniotic membrane, in addition to the chorion, allantois, and yolk sac was a major step that allowed vertebrates to reproduce in a terrestrial environment. Many vertebrate species are oviparous meaning fertilized eggs are laid outside the body, whereby embryos can complete development through an external incubation period. In viviparous species, the embryo completes development (or nearly so) inside the mother's reproductive tract (see the image on left forcomparison of the two). Viviparity has evolved independently in multiple lineages "in at least 142 occasions in vertebrate history" (Blackburn 1999). It is exhibited within multiple groups including sharks, caecilians, anurans (frogs and toads), salamanders, snakes, lizards, and mammals.

Female accessory sex organs of the reproductive system evolved along with the amniotic egg. The accessory organs transitioned from a "simple tube-like structure present at embryogenesis that develops into a specialized oviduct in oviparous species…" or as in eutherian mammals "…a highly vascularized structure for supporting complete embryogenesis…" (Major et al. 2022). The eutherian mammals (of which humans are a member) are characterized by having a placenta that supports embryonic development, contrasted from monotremes (oviparious mammals) and marsupials (embryos develop in a specialized pouch). The female reproductive tract of eutherians is also distinct when compared to the other tetrapods, a group whose members include mammals, amphibians, birds, and reptiles. Those non-eutherian tetrapods have a common urogenital opening called a cloaca whereas eutherians have a separate complex perineal structure (Hall, Rodriguez-Sosa, and Plochocki 2017) that provides compartmentalization for increased complexity (Pavlicev, Herdina, and Wagner 2022).

Human female sex organs and genitalia

Key events in the development of the female reproductive tract unfold during embryonic development and puberty. Development is described in the previous chapter and the processes of puberty and sexual maturation are described in the chapter on the *Reproductive Cycle*. Much is still unknown about the evolution and functionality of female sex organs and genitalia, and as Sloan and Simmons (2019) point out, "traditionally, male genitalia have been the overwhelming focus of evolutionary studies". For female empowerment, we need a more complete knowledge of female evolution, anatomy, physiology, and so forth.

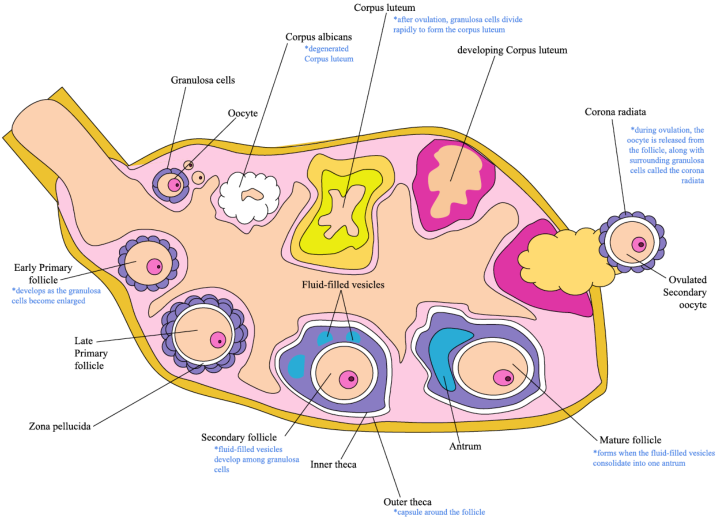
The primary sex characteristics and anatomical structures within the female reproductive system are discussed below, including ovaries, Fallopian tubes, uterus, cervix, vagina, and external genitalia.

Ovaries

A pair of ovaries is the site of oocyte development and the production and secretion of the steroid hormones estrogen, inhibin, progesterone, and testosterone. Each ovary is suspended in the pelvic cavity by a suspensory ligament (attached to the lateral margin of the ovary and extends to the lateral pelvic sidewall) and an ovarian ligament (connects the ovary to the side of the uterus). They are also attached to the peritoneal covering through the mesovarium which projects from the posterior surface of the broad ligament and attaches to the ovary. The mesovarium is a double-layered fold of the peritoneum (a thin membrane that lines the abdominal cavity and covers organs) that helps anchor and support the ovaries in their position within the pelvic cavity.

The ovaries are covered on the outside by a layer of simple cuboidal epithelium called germinal (ovarian) epithelium. Below the ovarian epithelium is a dense connective tissue capsule, called the tunica albuginea, a Latin term that roughly translates to “white coat”. It is so named because of its dense, white, fibrous appearance and it functions as a protective sheath.

Within can be found the inner medulla: a heterogeneous mix of immune cells, blood vessels, nerves, stem cells, and lymphatic vessels, all of which make up the ovarian interstitial stroma (Kinnear et al. 2020). A membrane, the basal lamina, separates the interstitial stroma from the functional units of the ovary known as the ovarian follicles. These lie within the outer cortex (Oktem and Urman 2010). The follicles are composed of oocytes surrounded by granulosa cells at various stages of development (details on follicles can be found in the Reproductive Cycle chapter). The diagram below illustrates an ovary with the follicles at varied stages of development.


Corpus luteum
*after ovulation, granulosa cells divide rapidly to form the corpus luteum
Corpus albicans
*degenerated Corpus luteum
developing Corpus luteum
Granulosa cells
Oocyte
Corona radiata
*during ovulation, the oocyte is released from the follicle, along with surrounding granulosa cells called the corona radiata
Early Primary follicle
*develops as the granulosa cells become enlarged
Fluid-filled vesicles
Ovulated Secondary oocyte
Late Primary follicle
Zona pellucida
Secondary follicle
*fluid-filled vesicles develop among granulosa cells
Inner theca
Antrum
Mature follicle
*forms when the fluid-filled vesicles consolidate into one antrum
Outer theca
*capsule around the follicle

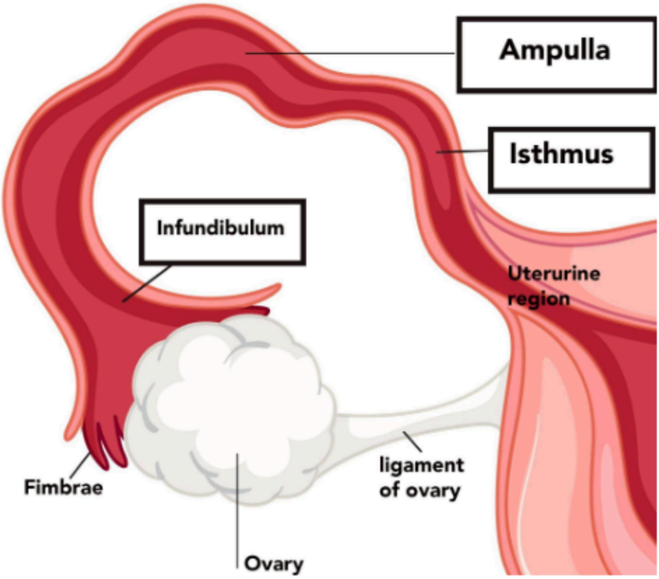
Illustrated anatomy of the ovary with oocyte development.

Oviducts (Fallopian tubes)

There are two oviducts (uterine tubes) approximately 7 to 12 cm long. One is associated with each ovary, also called the Fallopian tube after Gabrielle Fallopius (Mortazavi et al. 2013). These serve as conduits that receive mature ovum from the ovaries, the site for fertilization and transport of the zygote to the uterus.

Within the oviduct

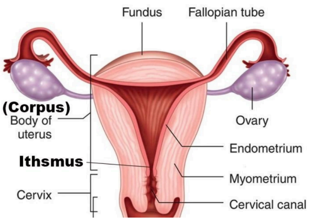
The oviduct is divided into four regions (from ovary to uterus) pictured below. 1) the infundibulum, which is surrounded by fingerlike extensions called fimbriae that are not directly connected to the ovary but "brush" the ovary; 2) the ampulla, 3) the isthmus and 4) the uterine region.


Ampulla
Isthmus
Infundibulum
Uterurine region
Fimbrae
ligament of ovary
Ovary

Ovary held into place by the ligament. Fimbriae of oviduct closest to ovary. Infundibulum opens into the ampulla and then isthmus. The oviduct is directly connected to the uterus.

The inner mucosal layer of the oviduct is composed of epithelial cells responsive to estrogen and progesterone. The epithelial tissue on the inner surface of the oviduct is comprised of two main cell types: ciliated epithelial cells and nonciliated secretory epithelial cells. A muscular layer lies between the inner mucosa and the contractions of this muscular layer work in conjunction with cilia movements and tubal secretory fluids to achieve ovum transport along the length of the oviduct (Sokal 2011).

Uterus



Internal female reproductive organs.

Anatomy of the uterus.

The uterus is a fibromuscular organ with an endometrial lining that functions by preparing for and ultimately supporting the embryo. As the embryo grows and matures, the uterus expands to accommodate the developing fetus.

There are three main parts to the uterus, cervix, fundus, and main body. Ovaries and fallopian tubes have been omitted for emphasis.The endometrium varies greatly depending on the phase of the menstrual cycle. The proliferation of the endometrium occurs under the influence of estrogen; maturation occurs under the influence of progesterone. Details are provided in the Reproductive Cycle chapter.

Humans have a pear-shaped uterus suspended by several ligaments, including the utero-ovarian ligament, round ligament, broad ligament, cardinal ligament, and uterosacral ligament. The uterus is further supported (inferiorly) by the pelvic diaphragm, urogenital diaphragm, and perineal body. The size varies tremendously depending on hormonal status, pregnancy, and prior pregnancies.

The uterus subdivides into four main anatomic segments (from superior to inferior): the fundus; a broad curved area in which oviducts connect to the uterus, the corpus (body); the main part of a uterus, and it starts directly below the level of fallopian tubes and continues downward, the isthmus is a lower neck region of the uterus, and cervix; which extends downwards from the isthmus and opens in the vagina.

In addition to the endometrial layer, the uterus has a muscular layer that lies beneath (myometrium). The outer surface is covered by a thin epithelial layer (perimetrium) known as the serosa.

Cervix

The cervix is a fibromuscular organ that protrudes into the uterine cavity and down to the vagina, (linking the two together). It contains columnar epithelium that produces cervical fluid secretion which varies dramatically in response to estrogen (Levin 2003). At the upper end of the endocervical canal at the junction with the uterine cavity is the internal os, and the external os is the opening of the cervix within the vagina. Above the external os lies the fusiform endocervical canal, approximately 2 cm long and lined with columnar epithelium and endocervical glands. The intersection where the squamous epithelium of the exocervix and columnar epithelium of the endocervical canal meet, the squamocolumnar junction, is dependent on hormonal stimulation and is also known as the transformation zone (Sokal, 2011).

Vagina

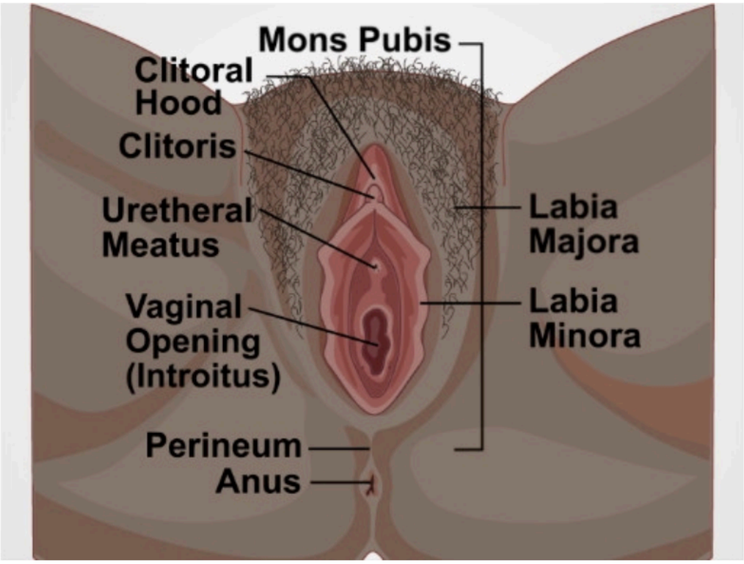
The vagina is an elastic, muscular tube connected to the cervix proximally and extends to the external surface through the vulva vestibule. The vaginal opening is located posterior to the urethra opening. The vagina has many functions: to act as a reservoir and passageway for semen during sexual intercourse, an exit for menstrual blood, a sensitive area for sexual stimulation; and a birth canal for the passage of the baby from the uterus. The vaginal wall consists of three layers: a) an inner mucous-type stratified squamous cell epithelium supported by a thick lamina propia, that undergoes hormone-related cyclical changes, b) the muscularis composed of outer longitudinal smooth muscle fibers and inner circular fibers, and c) an outer fibrous layer, rich in collagen and elastin, which provides structural support to the vagina.

Vaginal lubrication during sexual stimulation

Lubrication is needed to promote sexual pleasure however the vagina's lubrication does not come from glands but from a transducive fluid expressed through vaginal epithelial cells with the aid of nitric oxide (NOs) (Levin, 2003). The exact mechanism is not completely understood but research indicates that estrogen promotes both blood flow and NOs and the transducate is produced when the blood vessels of the lamina propria become engorged during sexual arousal creating pressure (Musicki et al. 2009).

The Vulva

The vulva, illustrated below, describes the external female genitalia: mons pubis, labia majora, labia minora, clitoris, and vulvar vestibule.


Mons Pubis
Clitoral Hood
Clitoris
Uretheral Meatus
Vaginal Opening (Introitus)
Perineum
Anus
Labia Majora
Labia Minora

Anatomy of the vulva.

Mons pubis

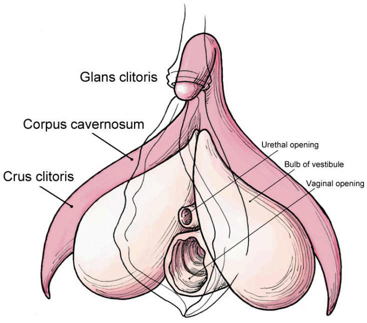
The mons pubis is a mound of adipose tissue located directly anterior to the pubic bones. Upon puberty, it becomes covered in pubic hair. According to Nguyen and Duong (2022) the mons pubis functions as a source of cushioning during sexual intercourse. The mons pubis also contains sebaceous glands that secrete pheromones to induce sexual attraction.

The Labia Minora and Majora

There are two pronounced folds of fibroadipose tissue that protect the opening of the vagina which looks like lips called labium, the outer is known as the labia majora and the smaller, inner is known as the labia minora. The inner surface of the labia majora and labia minora lack hair follicles or sweat glands but contain many sebaceous glands that release sebum onto the skin surface. The labia minora are derived from the same tissue as in males and share homology with the penile urethra and part of the skin of the penis in males. The labia minora is composed of dense connective tissue, erectile tissue, and elastic fibers and "laterally, they extend obliquely from the clitoris toward the rear for about 4 cm on either side of the vaginal orifice" (Deliveliotou and Crestas 2006). The fourchette is where the labia minora meet, and below this is the perineum that ends at the anus.

The Clitoris

The clitoris whose etymology may be traced back to the Greek noun "kleis" which means key, is located at the top of the vestibule and has been identified as "the most critical anatomical structure for female sexual arousal and orgasm" (Pauls 2015). As Masters and Johnson (1966) famously wrote in their book Human Sexual Response, "the clitoris is truly unique in the human organ system in that its only known function is that of serving as an erotic focus for both afferent and efferent forms of sexual stimulation". There is a great deal of size variation in the clitoris and this variation is greater than penile size variation (Wallen and Lloyd 2011). The first comprehensive study of the clitoris was not completed until 1998 by O'Connell et al. (1998).



Anatomy of the clitoris. Outline shows unaroused state compared to aroused.

The clitoris, illustrated on the right, is tri-planar with three main parts: the **glans clitoris** (external); two **crura** extending down from the glans and deep into the vulva, where the corpora are located; two **bulbs** that extend on either side of the vagina. Variation in the size and shape of the clitoris exists (Longhurst et al., 2023). The visible portion of the clitoris is a small rounded tubercle (glans clitoris) with many nerve endings and is highly sensitive to touch. The majority of the clitoral anatomy is internal. "The body (corpora) of the clitoris consists of two cylindrical corpora cavernosa composed of thin-walled, vascular channels that function as erectile tissue" (Deliveliotou and Crestas 2006). Both the corpora and glans are homologous to the corpus cavernosa and glans of the male penis (Shih, Cold, and Yang 2013). There are also a pair of bulbs, "the bulbs of the clitoris", that are contiguous with the glans and corpora of the clitoris that engorge with blood during sexual arousal (O'Connell et al., 1998). Along with the glans, the internal areas are also erotically responsive. The urethra lies surrounded by this complex and extends from the bladder to the outside of the body for the excretion of urine.

Longhurst et al., (2023) note that "historically the stigma and lack of understanding of the function of the clitoris led to the justification and, unfortunately, the performance of clitoridectomies (removal of the clitoris) as a treatment for insanity, epilepsy, catalepsy, and hysteria." Unfortunately, clitoridectomies and other types of injuries to female genital organs, known as female genital mutilation, are still performed worldwide (Molina-Gallego et al., 2021).

Q&A with Prof. Helen E O'Connell AO ,MD MMed FRACS FAICD,

Officer (AO) in the General Division of the Order of Australia, Urological Surgeon

Professor Helen O'Connell, MD.

What drew you to study Urology and specifically female genitalia? Urology was definitely a source of great mystery. We had relatively minimal teaching throughout our medical degree. As a young doctor, I was encouraged to look at specialty surgery rather than general surgery, which was regarded as 'dead' prior to the rise in laparoscopic surgery. As a young resident, I recall female patients being delighted to have a woman to talk to about their urinary problems. For the first time, it wasn't an advantage to be female! Our textbook- Lasts

Anatomy was full of factual errors and omissions when it came to the description of the female perineum. The use of pejorative language, paucity of diagrams, and outright omission of the clitoris made me angry at first, I was even suspicious about the nature of Anatomy as a science. It appeared that social factors were dominating the discourse.

What have you enjoyed most about your research? The journey itself is a great unknown with the unthinkable evolution of the science and art of female anatomy over my career. The 3-D models based on MRI studies as well as cadaveric studies bring the Anatomy to life. Literally, you can hold the anatomy in your hands. Designers, artists, and prominent speakers are forging, a community-based movement, fed by accurate science that is empowering, both women and men. Understanding the relationship of the clitoris to the vulva, vagina, and urethra is now tangible through good images. This helps women and girls understand their bodies in a way that is wholesome and promotes better health. None of this was foreseeable.

What did you find most challenging about your career? Managing time is probably the most challenging aspect. There is a significant call on a reasonably finite resource and ensuring all of my priorities are looked after takes some doing.

What advice do you have for future women scientists? Get the best training that you can. Do work that will distinguish you from others in a good way. Don't be too worried about burnout. It will happen and you'll recover with a good two-week break. Choose good mentors. As you rise up, look after your staff and your mentees and treat everyone with respect. Make time for family, friends, and fun.

Skene's Glands

Homologous to the prostate in the male, these are branched, tubular glands, adjacent to the distal urethra. Dwyer (2012) reports that the location of Skene's glands is in an area designated as the Grafenberg spot (G spot) which has been anecdotally associated with stimulation and ejaculation during orgasm.

Vulvar vestibule

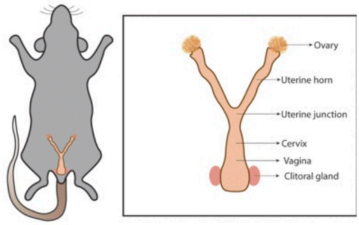
Just posterior to the glans clitoris lies the vestibule. This extends to the fourchette of the labia minora. The vestibule contains the vaginal opening and is bordered by the edges of the labia minora.

The Bartholin's glands also known as the greater vestibular glands

There are two "pea-sized glands located symmetrically at the posterior region of the vaginal opening... which are involved in "mucus secretion and vaginal lubrication. Cyst formation in the glands is common and results from mucus build-up in gland ducts" (Yee and Goldstein 2023).

Variation of mammalian reproductive tracts exists

All female animal reproductive tracts are derived from the Müllerian ducts in the embryo, however, the mammalian female reproductive tract is much more complex when compared to other animals and exhibits diversity across mammalian species (Major et al. 2022). It is through "species-specific differences in Müllerian duct fusion at the midline, growth, and differentiation" that these distinct morphologies arise (Machado, Ontiveros, and Behringer 2022). As illustrated in Kobayashi and Behringer (2003), there are three distinct general morphologies: duplex without a vagina, duplex with vagina or simplex. The duplex uterus is divided into two separate horns that each have separate cervices whereas the simplex uterus has a single chamber. Examples of variation are seen from monotremes through higher primates. Marsupials have duplex uteri with two vaginae; rabbits, rodents, pigs, and marine mammals-duplex uteri with a single vagina (seen below), and higher primates have a simplex uterus.



A duplex uteri is found in mice. Image modified from Chumduri and Turco, 2021.

The mammalian female reproductive tract can be considered an evolutionary marvel having undergone significant adaptations and complexities over millions of years. Viviparity, placental development ovulation control, and behavioral complexities are just some of the key adaptations involved in the reproductive tract that have contributed to mammalian success and the great diversification from the early Cretaceous era onward.

Think, Pair, Share

Come up with a list of reasons that there has been a limited amount of research done on the female sex organs and genitalia as compared to the male genitalia.

Discuss reasons why women are not well informed about their sex organs and external genitalia.

Why might there be variation in the structure of the uterus across mammalian taxa? E.g. simplex and duplex?

Across animal taxa, females and males have different sex organs but what other ways are they different?

Deeper Questions

Echidnas and platypus are monotremes and diverged from the eutherians around 187 million years ago. Explain why monotremes provide the key to understanding how viviparity evolved in mammals.

A survey conducted in 2020 of 2,000 women found that nearly 25% misidentified the vagina and 46% could not properly identify the cervix. How can this be rectified?

In an article by Wahllquist published in the Guardian (2020) “The sole function of the clitoris is female orgasm. Is that why it’s ignored by medical science?” Urologist Helen O’Connell (who completed the first comprehensive anatomical study of the clitoris) was interviewed and said “female anatomy should be considered equally alongside male anatomy”. Why is this so important and what challenges still exist that hinder this?

Key terms

Ampulla
Bartholin’s glands
Cervix
Clitoris

- Corpus cavernosa
- Crura
- Endometrium
- External os
- Fallopian tubes
- Fimbriae
- Glans clitoris
- Infundibulum
- Inner medulla
- Internal os
- Isthmus
- Labia majora
- Labia minora
- Mesovarium
- Mons pubis
- Myometrium
- Outer cortex
- Ovaries
- Oviduct
- Oviparity
- Perimetrium
- Skene’s glands
- Transformation zone
- Tunica albuginea
- Uterus
- Vagina
- Vestibule

Viviparity

Vulva

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Suggested Readings

"The Female Reproductive System: An Anatomical and Histological Atlas" by Konrad Stender, Rainer Winkelmann, and Jürgen Görtz – This atlas provides detailed anatomical and histological illustrations and descriptions of the female reproductive system, making it a valuable resource for understanding its structure and function.

"The Vagina Bible: The Vulva and the Vagina: Separating the Myth from the Medicine" by Dr. Jen Gunter – Dr. Jen Gunter's book is a comprehensive guide that covers everything you need to know about the female reproductive tract, debunking myths and providing evidence-based information on vaginal and vulvar health.

"She-ology: The Definitive Guide to Women's Intimate Health. Period" by Sherry A. Ross – The author is a leading ob-gyn, educator and women's health advocate, Ross addresses every urgent, confounding, culturally taboo or embarrassing question women have about vaginas

"Our Bodies, Ourselves" by the Boston Women's Health Book Collective – While not exclusively focused on the female reproductive tract, this classic book covers women's health comprehensively, including detailed information about reproductive anatomy and health.

Interesting Podcast

Ologies with Alie Ward Gynecology (NETHER HEALTH) with Philippa Ribbink

4.

SEXUAL SELECTION

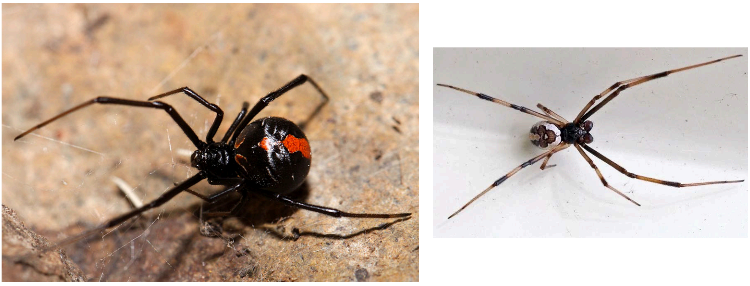
STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Summarize the theory of sexual selection and contrast it with natural selection
- Describe the connection between anisogamy and sexual selection
- Recall examples of sexually dimorphic traits under the influence of sexual selection
- Explain how sexual conflict could result in the coevolution of female and male genitalia
- Debate the biological and cultural underpinnings of sexually dimorphic traits in humans

Uncovering the mystery of self-sacrificing male spiders

While completing her graduate studies at Cornell **Maydianne Andrade** studied red-back spiders (*Latrodectus hasselti*) and asked the question: why would a male somersault onto the female's fangs ensuring their death? Andrade found that this is part of their courtship and although it leads to the death of the male, females are more likely to copulate with males that engage in this courtship. More importantly successful copulation is dependent upon this death-inviting behavior. Therefore somersaulting to their death is the best way to ensure mating success because, without cannibalism by the female, the male redbacks would never be able to pass on their genes to the next generation (Andrade, 1996; 2003). Dr. Andrade has continued her research and has become the expert on sexual selection and mating behaviors in widow spiders at the University of Toronto Scarborough.



Female red-backed spider on left, male red-backed spider on right. Note the male is smaller than the female.

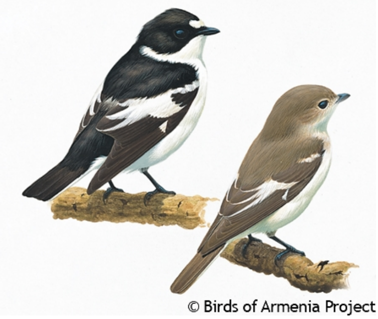
What is sexual selection?

Instead of natural selection as the driving force resulting in the observed death-wish-behavior of male red-backed spiders, a different type of selection – sexual selection has been influencing this trait. Darwin found this type of behavior as well as other traits that seemingly defied natural selection as perplexing. For example, he notoriously was confounded by the male peafowl's (peacock) elaborate feathers and loud calls because he thought such flashy traits would reduce an individual's fitness. Darwin recognized the female peafowl's coloration was much duller, and they did not make loud calls. The striking difference between the peafowl sexes is an example of sexual dimorphism. Dimorphism was first documented by Wallace who observed *Papilio memnon* butterflies, whereby the females looked very different from the males (Wallace 1865). But why do females look and act differently than males in many species? It stands to reason that such conspicuousness in males would significantly increase the risk of predation. Under natural selection, these traits should not evolve because they appear to reduce fitness yet they persist.

Peacocks have highly visible elaborate plumage to attract female peahens.

After much thought and accumulation of data Darwin understood the differences among peafowl sexes in coloration and behavior were examples of characteristics that had evolved thanks to what he called "sexual selection" rather than natural selection. He put forth this theory in his book “The Descent of Man, and Selection in Relation to Sex” (1871). Darwin explained there is variation among males, and some males are better than others at attracting mates in rivalry with other males, and “would consequently have left a larger number of offspring to inherit their newly-acquired beauty.” Variation in coloration, ornament, and or behavior could provide an advantage in acquiring mates and if heritable, these traits would be passed on at a higher frequency. In this way sexual selection is similar to natural selection however it is explicitly driven by competition for mates and preferences in choosing mates for reproduction. Thus sexual selection is different from natural selection because “the males have acquired their present structure, not from being better fitted to survive in the struggle for existence, but from having gained an advantage over other males, and from having transmitted this advantage to their male offspring alone” (Darwin, 1871). As Weismann points out individuals with certain sexually dimorphic traits can benefit because they “gain an advantage in the struggle for existence by their new characteristics” (1872). Sexual selection focuses completely on increasing fitness through successfully reproducing with a mate. When individuals differ in their reproductive ability and there are a limited number of opportunities to mate with another this creates competition, and if these differences are heritable then selection is at work. Shuker (2010) remarks that “sexual selection is the relationship between a trait and its effect on fitness through sexual competition.”

Sexually selected traits persist even when they may result in increased predation or harmful risky behavior because ultimately mating success is more important than living long. These traits increase an individual's chance of attracting mates and so are sexually selected. There are numerous examples of sexually dimorphic traits which can be explained by sexual selection such as the white patch on the forehead of a male collared flycatcher (Ficedula) pictured here. Female collared flycatchers lack the patch and have a dull brown and white plumage. They are more inconspicuous. It turns out that the size and brightness of the male's forehead patch is positively related to their reproductive success so that is likely the reason it persists (Gustafsson, Qvarnström, and Sheldon 1995).


© Birds of Armenia Project

Collared flycatcher male (left) and female (right). Image from the Birds of Armenia Project.

Darwin suggests two avenues for the evolution of sexually dimorphic traits

1. Mate choice. Individuals of one sex select among individuals of the other sex (also known as intersexual selection). How an individual chooses a mate can be based on various signals from the suitor. These factors can be taken as indications of genetic superiority, direct benefits provided to the mate, or they evoke a positive association known as sensory bias. Those of one sex can showcase signals or provide benefits in various ways.

Examples of traits considered to be sexual selection factors involved in mate choice.

- Ornamental traits
  - Example: the intense blue plumage of male Hainan blue flycatchers Cyornis hainanus, (Dale et al. 2015), or the ornamental skin folds found on female pipefishes (Nerophis ophidion) during spawning season (Rosenqvist 1990)
- Vocalizations
  - Example: long, loud calls exhibited by Pacific tree frogs, Psuedacris regilla (Vélez and Guajardo 2021)
- Courtship displays to attract mates
  - Example: dancing peacock spiders, Maratus (Girard, Elias, and

Kasumovic 2015)

- Providing direct benefits to potential mates to persuade them to be chosen
    - Example: male scorpionflies (Hylobittacus apicalis) bring prey items to females during courtship as "nuptial gifts" and if the item is not "large enough" she will reject him (Thornhill 1984)

2. Mate competition. When there is a limited number of mates, those of the opposite sex must compete with one another for the opportunity to gain access and mate with the other sex (also known as intrasexual selection).

Examples of traits considered to be sexual selection factors involved in competition.

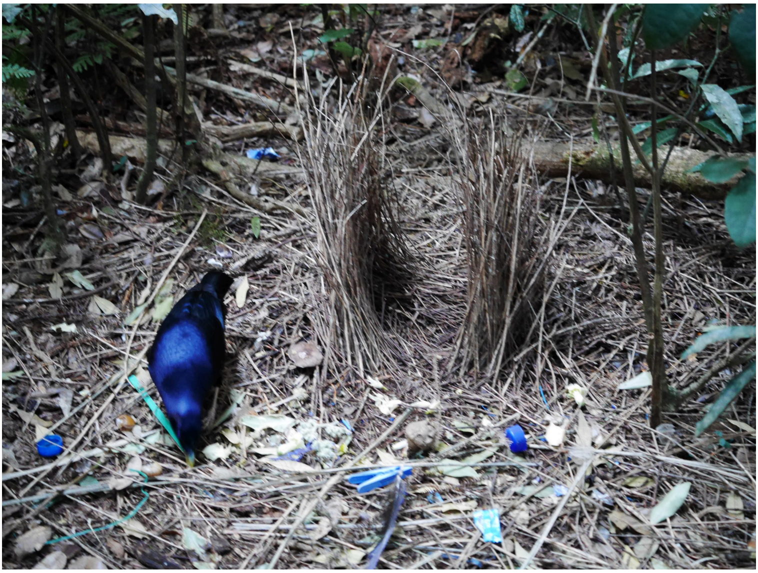
- Aggressive displays

    - Example: female gobies, Pomatoschistus minutus, exhibit aggressive female-female interactions when there are a limited number of males to mate with (Kvarnemo, Forsgren, and Magnhagen 1995); in territorial barking geckos (Ptenopus garrulus) larger males exhibit more aggressive behavior and are more likely to breed (Hibbitts, Whiting, and Stuart-Fox 2007)
- Physical combat
    - Examples include: repeated sequences of ritualized grappling between male Gila monster lizards, Heloderma, (Gienger and Beck 2007); male big horn sheep fighting with one another for access to females, body mass and horn size are positively correlated with reproductive success of mature males (Coltman et al. 2002)

- Acquiring and defending territories that members of the opposite sex use
    - Example: red-winged blackbird, Agelaius phoeniceus, females prefer males defending superior territory (Yasukawa, Blank, and Patterson 1980)
- Sperm competition and baculum structure in species where females mate with multiple males
    - Example: a meta-analysis of several bird species found that sperm competition favored larger males in dense populations, (Møller and Ninni 1998). Andre et al., (2020) found that in house mouse populations the rate of multiple paternity can reach up to 70% indicating strong male-male competition. They also found that male mice have a boney structure in their penis (baculum) which

provides stimulation to the female reproductive tract and varies in width among males. Their research shows that baculum size covaries with cervix size and contributes to male reproductive success.

Two sexes have different selection pressures operating because of anisogamy



Male Satin Bowerbird tending his bower by placing various eye-catching objects he has collected. Females mate with males based on how well-constructed and decorated the male has made the court.

Both mate choice and mate competition avenues of sexual selection are attributable to anisogamy, whereby females produce fewer larger gametes compared to males (as discussed in the chapter on the *Evolution of Sex*). Every egg is much more valuable compared to sperm because of both its size and its relative scarcity. Anisogamy creates competition among males for access to females during mating and females are likely to be the choosier sex because of the investment they have made in their eggs (Bateman 1948). Therefore traits will evolve differently under sexual selection among the sexes. For example, the male Satin Bowerbird (Ptilonorhynchus violaceus) of eastern Australia (see image on right) engages in complex behavior involving multiple traits such as building, and decorating stick structures called bowers where they court females (Borgia 1985). According to Borgia (1995) "females exert strong preferences in mating, and only a small proportion of males achieve most of the matings. Males with high-quality bowers with symmetrical walls formed from thin, densely packed sticks, many decorations on their courts mate most."

The roles can be reversed when the circumstances change-as in the case of pipefishes and seahorses where the males are more choosey and the females must compete with one another for mates (Vincent et al. 1992). More importantly, there has been a research bias towards only studying male behaviors and traits. This male-focused bias by past evolutionary biologists has skewed our understanding of sexual selection making it appear as though secondary sexual characteristics are only found in males and not in females (Cooper et al. 2019). However, new research examining female behavior and traits is producing findings expanding our understanding of this topic. For example, there are bird species in which females, like males, have noticeable dimorphic characteristics such as brightly colored plumage or pelage and elaborate ornaments as discussed by Clutton-Brock (2009). It is also notable that "females—just as males—typically benefit from having more than one mating partner" and "positive selection for mate acquisition may potentially be common in females" as in males (Fromonteil et al., 2023).

What about sexual conflict?

Sexual selection operates differently in females and males because of anisogamy. Sometimes because of these differences **antagonistic coevoltion** between the sexes occurs and traits that evolve in one sex have become harmful to individuals of the other sex. Holland and Rice (1997) posit that "intersexual conflict over mating rate will continually select for new, or more elaborate, traits in males that cause females to mate at a rate beyond their optimum, and for females to evolve counter-adaptations." An example of intersexual conflict has been observed in ducks where their genitalia have coevolved in opposite directions (Brennan, Clark, and Prum 2009). Forced copulations (males forcefully mating with females unwilling to mate with them) are common among waterfowl and enhanced by males' corkscrew-shaped penis. These forced copulations "result in overt sexual conflict between males and females to control fertilization…" and consequently, female waterfowl have evolved "…blind-ending pouches and a series of spirals that are opposite to the chirality of the corkscrew-shaped penis" (Brennan, Clark, and Prum 2009). Moreover, the counter-penile-shaped female vaginas have evolved despite "the indirect genetic benefit of being fertilized by preferred males" (Brennan and Prum 2015).

Q&A with Dr. Patty Brennan, Ph.D.

Associate Professor at Mount Holyoke University

Dr. Patty Brennan, PhD.

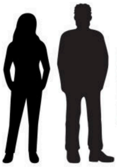
What drew you to studying sexual selection and specifically waterfowl genitalia coevolution? I find the idea that sexual behavior can drive so much amazing evolutionary change really compelling, and genitalia are an excellent example of how these dramatic changes can happen given their primary function during copulation. I became interested in bird genitalia after I realized that the birds I was studying for my PhD (tinamous) had penises. Since I had never even heard that some birds had penises, I wrote a postdoctoral proposal to investigate why birds had lost their penis, and why some of the species that kept them had such exaggerated morphologies. At the time I was not thinking about coevolution, but as soon as I dissected my first duck penis, I predicted that female ducks should have some interesting vaginas too, and when I looked that is exactly what I found. I realized right away that female genitalia were vastly understudied, and have been making an effort to look at both males and females ever since.

What have you enjoyed most about your research/fieldwork? Being the first person to open up a research area first studying tinamou reproductive behavior, and then genital coevolution in vertebrates has been very exciting! My recent research has expanded to look at female genitalia and clitoris morphology, and I enjoy being able to highlight the gaps, and then filling them in as I go along. Most amazing, I get to do this work at a women's college, where my students are particularly excited to contribute to science that equalizes our understanding of females in nature.

What do you find most challenging about your career? The topic of my research can be difficult to discuss with some people who are uncomfortable with conversations that involve frank discussion of genital parts and sexual behavior. I try to mitigate this problem by doing a lot of outreach to make the point that genitalia and sexual behavior are integral and crucial parts of an organism's biology and not something that we should have taboos about. I also had challenges with raising a family while trying to have a permanent job. I ended up prioritizing my family, and as a result, I spent several years in non-tenure track positions, before getting my permanent position now. It all worked out in the end, but it reminded me of the saying that we can have it all, just not at the same time. Being a Hispanic immigrant was difficult at times because of microaggressions, but I have become better at pointing out behaviors that are hurtful rather than internalizing them.

What advice do you have for future women scientists? Ask for a raise. Keep your friendships alive. Find projects that are exciting for you, but don't let your life outside of academia suffer because of your scientific passion. Make the time to take care of yourself, be social, learn a new skill, practice a sport, whatever fills you up. If you have a partner, have difficult conversations about how to support each other in your chosen careers, and what you need from them, and be ready to renegotiate constantly. Trust yourself and look for senior allies wherever you are. Become familiar with your Title IX offices and the procedures to report behavior that is not appropriate. Support other women.

Sexually dimorphic traits in humans



Adult women are different than men. Besides genitalia, several traits **generally** exhibit sexual dimorphism. Hormonal differences underlie these traits. Yet these differences are "on average", there is significant individual variation, and not all individuals will conform to these patterns. Moreover, cultural gender norms augment the differences.

Traits in which adult females and males differ (on average).

Body hair: as mammals, we are covered in body hair but the "fine and short nature of our body hair renders most of it invisible…The retention of visible head, axillary, and pubic hair remains a conundrum for anthropologists and evolutionary biologists alike" (Ramsey et al. 2009). Overall, facial hair is less noticeable in women compared to men because androgens are involved in hair production. Lower DHT levels resulted in decreased facial and body hair (Imperato-McGinley et al. 1993).

Breast size: on average women have larger breasts than men. However, breast size and shape can vary significantly. A study by Anderson et al. (2013) examined 342,000 individual breast size measurements from 108 different countries and found the shape of the female breast varies to some extent depending on the country of birth.

Body fat composition: females have greater body fat composition than males (Wells 2007). Boulet et al. (2022) note that "a critical level of fat in women is necessary for menarche and for the recovery of menstrual cycles after energy restriction."

Muscle mass: males have greater total lean mass than females (Wells, 2007) and females have a greater proportion of type I muscle fibers (Haizlip, Harrison, and Leinwand 2015). These are known as slow-twitch fibers and are often observed in greater abundance in endurance athletes.

Skeletal differences: females have lower bone mass density than males due to differences in the width/thickness of bone (yet gender-related differences in bone size are related, in part, to different types of physical activity) (Nieves et al. 2005). Lewis et al. (2017), comment that the "female pelvis tends to be wider and broader, with less prominent ischial spines… that allow for a wider pelvic aperture in females which functions as the birth canal, facilitating the passage of large-brained neonates."

Another notable difference has been found in knee alignment, specifically in the quadriceps angle (Q-angle) which represents the angle formed by a line from the anterior superior iliac spine of the pelvis to the patella center and a line from the patella center to the tibial tuberosity (Livingston 1998). The Q-angle impacts the "quadriceps mechanism on the knee, it also gives an idea how the thigh muscles function to make the knee move, as well as how the knee patella tracks in the groove of the knee joint"… females have higher mean values (Khasawneh, Allouh, and Abu-El-Rub 2019). This is a risk factor for anterior cruciate ligament injury, explaining why women experience significantly more ACL tears than men (Harmon and Ireland 2000).

Auditory differences: females as a group have greater hearing sensitivity and greater susceptibility to noise exposure at high frequencies than males as a group (McFadden 1998).

Does sexual selection occur in human populations?

There are aspects of humans that fit the model of sexual selection of females being more choosy and males more competitive with one another for mates. This would lead to sexually dimorphic traits involved in reproduction. The investment in offspring through gestation and nursing is significantly greater for women than men. There is also evidence for sperm competition in men. Both are factors that influence sexual selection. Several lines of evidence support sexual selection as an important evolutionary force in humans (Puts 2010; Lindenfors and Tullberg 2011; Puts 2016). Arguments against the role sexual selection plays are made as well. Schacht and Kramer (2019) note that paternal investment by humans is significantly greater as compared to our closest relatives and rather than polygyny and/or polyandry that would drive male-male competition, monogamy is the rule rather than the exception. Overall, caution must be taken due to the complexity of human reproduction and to avoid stereotypes associated with the simple dichotomy of choosy women and competing men. There are a multitude of possible explanations for the persistence of sexually dimorphic traits.

Could the female orgasm be a result of sexual selection?

Humans are placental mammals, also known as eutherians, but the human reproductive tract is not entirely representative of all eutherians. Diversity in female sex organs and genitalia exists within the group. For example, elephant shrews lack a cervix and true vagina whereas anteaters and sloths have a utero-vaginal canal (Pavlicev, Herdina, and Wagner 2022). Many mammals have a duplex uterus consisting of two cornua that join distally into a single body such as mice, cats, dogs, and pigs. Interestingly some species exhibit genital variation within members. For example, cetaceans (dolphins, porpoises, and whales) have vaginas with muscular protrusions of the vaginal wall into the vaginal lumen that vary in number, shape, size, and positioning across species (Orbach et al. 2018). In many instances, natural selection is likely responsible for producing adaptations that increase fitness. However, when it comes to cetacean vaginas, Orbach et al., (2017) posit that the observed variation could have been "shaped by post-copulatory sexual selection". Sexual selection is now widely recognized as an important selective pressure acting on genital morphology (Hosken and Stockley 2004; Simmons 2014; Sloan and Simmons 2019).

The female orgasm is not directly tied to reproductive success, unlike the male orgasm which always results in ejaculation. Shirazi et al. (2018) found in a recent survey of over 1,400 women, that over 20% never experience an orgasm during penile-vaginal intercourse. Furthermore, the majority of women surveyed reached orgasm without penile-vaginal intercourse but with assisted clitoral stimulation. Why might females experience orgasm without sexual intercourse? This is a debated topic and there are several hypotheses regarding the evolution of the female orgasm (see Lloyd 2005) but one in particular points to mate choice under sexual selection.

Research suggests that orgasm for women may signal a high-quality mate. Ellsworth and Bailey (2013) found that a woman's orgasm frequency and intensity were related to partner ratings of monetary investment and level of physical protection. Additionally, surveys indicate that orgasm is the "most important single predictor of sexual satisfaction for women" (Kontula and Miettinen 2016). Thus females may choose to have repeated sex with males with whom they experienced orgasms based upon the induced associated pleasurable sensations. Gallup Jr., Towne, and Stolz (2018) found a direct link between sexual satisfaction by women and the intensity of their orgasms and how many orgasms they had per encounter. Sperm competition may also be a driving factor in the evolution of the human female orgasm. The female orgasm may have the ability to improve sperm transport in the female reproductive tract to promote fertilization. Pavličev and Wagner (2016) note that the female orgasm "also causes patterns of brain activation and hormone release associated with increased uterine contractions, lower uterine pressure, and movement of semen into the uterus". Specifically, in addition to oxytocin, prolactin and luteinizing hormone surges accompany the human female orgasm which is similar to mammals that undergo copulation-induced ovulation, potentially linking the human female orgasm to an ancestral ovulatory function (Pavličev and Wagner 2016).

Sexual selection has played a significant role in a wide array of taxa, shaping various aspects of female biology, including mate choice, reproductive anatomy, behaviors, and communication. It has led to the evolution of traits and strategies that enhance a female's reproductive success and ensure the transmission of her genes to the next generation.

Think, Pair, Share

Besides food what might be some examples of direct benefits that mates of one sex could provide to those of the limited sex during courtship?

Find examples of phenotypic traits that you predict to be under the influence of sexual selection. Provide reasoning to support your answer.

In species where both sexes exhibit bright coloration/ornamentation is sexual selection responsible? Why or why not?

Do you consider the theory of sexual selection to be controversial? Why or why not.

Deeper Questions

As Ah-King (2022) notes, “the history of sexual selection research shows prevalent male precedence—that research starts with the male-centered investigation”. Why might this have led to misunderstandings about sexual selection?

What aspects of human behavior might be explained by sexual selection and what alternative explanations might there be for these?

In their article “Challenging Darwin’s Theory of Sexual Selection” (Roughgarden 2007) Joan Roughgarden contends that because of Darwin’s incorrect assumptions about gender and sexuality, the theory of sexual selection should be replaced with what they call social selection. Provide a list of pros and cons of their proposal.

Key Terms

Intersexual selection
Intrasexual selection
Sexual dimorphism

Sexual conflict

Sexual selection

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Suggested Reading

"The Red Queen: Sex and the Evolution of Human Nature" by Matt Ridley – While not solely focused on sex determination, this book explores the broader topic of sexual selection and the evolution of human behavior and characteristics. It provides insights into the evolutionary forces that shape sex and reproduction.

"The Mating Mind: How Sexual Choice Shaped the Evolution of Human Nature" by Geoffrey Miller – Geoffrey Miller explores the idea that human intelligence and creativity have evolved as a result of sexual selection, proposing that the human mind itself is a product of mate choice.

“Sexual Selection and the Origins of Human Mating Systems” by Bernard Chapais – This book delves into the evolution of human mating systems and the role of sexual selection in shaping human social and reproductive behaviors.

“The Evolution of Beauty: How Darwin’s Forgotten Theory of Mate Choice Shapes the Animal World—and Us” by Richard O. Prum – Richard O. Prum discusses Charles Darwin’s theory of sexual selection and explores how mate choice has led to the development of extravagant traits in various species, including humans.

“Sexual Selection: Perspectives and Models from the Neotropics” edited by Rodolfo Dirzo and John D. Terborgh – Focusing on the Neotropics, this book explores sexual selection in tropical ecosystems, featuring contributions from experts in the field.

“Sexual Selection and the Barn Swallow” by Anders Pape Møller – This book examines sexual selection in the context of barn swallows, offering insights into the role of mate choice in shaping the evolution of specific traits in this bird species.

“The Handicap Principle: A Missing Piece of Darwin’s Puzzle” by Amotz Zahavi and Avishag Zahavi – This book introduces the handicap principle, a concept related to mate choice and the evolution of costly signals used in courtship.

Interesting Podcast

The Science of Birds Female Birdsong

5.

REPRODUCTIVE CYCLE

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Explain the onset of puberty
- Describe how the HPG axis regulates the reproductive cycle
- Recall how the dominant follicle is recruited and ruptures
- Summarize the phases of the ovarian and menstrual cycle
- Illustrate the changes in hormone levels associated with the ovarian and menstrual cycles
- Predict how an increase/decrease in progesterone impacts the endometrial lining
- Compare and contrast estrus with menses

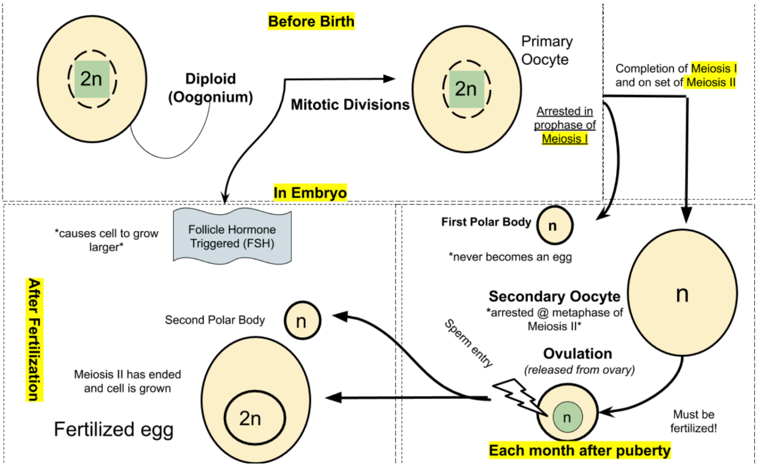
Historically, menstrual health has received little attention

Martha McClintock – researcher of human pheromones and menstrual synchrony.

As an undergraduate student at Wellesley College, biopsychologist Martha Kent McClintock examined how menstrual cycles become synced when women live close together. As Hermes (2022) contends, McClintock went on to write "what is likely the most famous honors thesis in history, which was ultimately published in Nature in 1971" and then to study the effect of pheromones on the cycle, showing how ovarian-dependent pheromones can regulate ovulation in women within a social group (Stern and McClintock 1998). In an interview by Natalie Angier in the New York Times (1998), McClintock postulated that the ability to pick up social cues and incorporate them into her cycle is beneficial because "reproduction is a very time-consuming, risky business, and the more cues a female has to her social setting, and whether this is the right time to try getting pregnant, the better off she'll be." McClintock's pioneering work provided insight into the complexity of women's reproductive cycles which are not only regulated by multiple endogenous controls (having an internal cause, e.g. hormones) but also impacted by exogenous factors (having an external cause, e.g. stress). However, a gap in our knowledge of women's reproductive cycle, specifically uterine and menstrual physiology, persists due to technical, scientific, and societal barriers (Critchley et al. 2020).

Intro to puberty and an overview of the hypothalamus-pituitary-gonadal axis (HPG)

All oocytes (female germ cells) for an individual mammalian female are produced before birth during embryogenesis. Recall from the Genetics of Sex chapter that the primordial germ cells arise early in development and migrate to the embryo's genital ridge. Duncan et al. (2020) review how the germ cells divide mitotically to increase in number and transform into oogonia as the differentiation into the female gonads occurs. After multiple mitoses, the oogonia become primary oocytes that enter meiosis, Prophase I, and remain dormant until puberty. Upon puberty, each month a subset of ovarian follicles mature and MII will resume at fertilization (see illustration below).

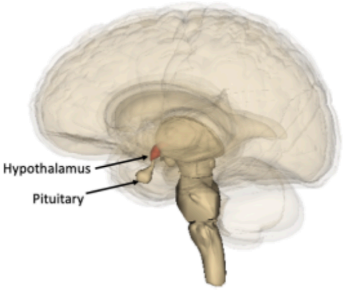

Before Birth
2n
Diploid (Oogonium)
Mitotic Divisions
Primary Oocyte
2n
Arrested in prophase of Meiosis I
Completion of Meiosis I and on set of Meiosis II
In Embryo
causes cell to grow larger
Follicle Hormone Triggered (FSH)
First Polar Body
n
*never becomes an egg
n
Secondary Oocyte
arrested @ metaphase of Meiosis II
After Fertilization
Second Polar Body
n
Sperm entry
Ovulation
(released from ovary)
Meiosis II has ended and cell is grown
Fertilized egg
2n
n
Must be fertilized!
Each month after puberty

Primary oocytes arise early in development and migrate to the embryo's genital ridge. These germ cells divide mitotically to increase in number and transform into oogonia as the differentiation into the female gonads occurs. Once puberty happens select secondary oocytes mature and are released each month.

Puberty is brought on by a complex series of events involving the endocrine system that concludes with sexual maturity. The endocrine system utilizes hormones to regulate and coordinate a wide range of physiological processes within the body. Hormones are chemical messengers produced by specialized glands and tissues, and they play a vital role in the development and maintenance of the reproductive cycle. This requires an intricate messaging system involving the brain and ovaries referred to as the **hypothalamic -pituitary-gonadal (HPG) axis**. It also involves the production of adrenal androgens which are hormones secreted by the adrenal cortex, the outer layer of the adrenal glands, situated on top of each kidney. Adrenal androgens including dehydroepiandrosterone (DHEA) and androstenedione contribute to the development of secondary sexual characteristics such as the growth of pubic and axillary (underarm) hair.

The HPG

At the base of the brain, under the thalamus, lies the pea-sized hypothalamus. The **hypothalamus** is highly specialized and coordinates the endocrine system. The hypothalamus functions in association with the **pituitary gland** to which it is attached (see image). The hypothalamus receives signals and has neurons that release hormones that travel to the anterior pituitary and trigger the release of other gonadotropins (hormones that regulate the activity of the gonads).



The hypothalamus connects to the pituitary gland by the stalk-like infundibulum. The pituitary gland consists of an anterior and posterior lobe, with each lobe secreting different hormones in response to signals from the hypothalamus.

The onset of puberty is marked by a reactivation of the HPG, which is suppressed during early childhood. Among the various hormones produced by the hypothalamus,

gonadotropin-releasing hormone (GnRH) is specifically involved in initiating the reproductive cycle. The onset of puberty occurs when "signals from the central nervous system and signals from the periphery indicate systemic health and adequate nutritional status converge in the hypothalamus to stimulate GnRH pulsatile secretion" (DiVall and Radovick 2008). GnRH binds to receptors in the pituitary gland stimulating the release of gonadotropins.

The age of onset varies widely among young girls ranging from 8-14 years of age. Both genetics and environmental factors are thought to impact the timing of pubertal onset (Uenoyama et al. 2019). Rubin et al. (2009) annually surveyed over 4,600 girls over a six-year timeframe (ages 8-12) and found a strong relationship between a mother's and daughter's age at menarche (the first period) suggesting a potential genetic factor. Another key determinant appears to be the amount of gluteofemoral fat a young woman has (Lassik and Gaulin 2007). This is because a certain threshold of fat cells is needed to produce enough **estrogen** to activate puberty and having sufficient body fat stores as the trigger for the reproductive cycle would be an adaptation "for ensuring that pregnancy will not occur unless there are adequate fat stores to sustain both the mother and the growing fetus" (Kaplowitz 2008). However different studies on the link between body fat and menarche provide conflicting results (Walvoord 2010).

Pulsating GnRH and the onset of puberty

The **preoptic area (POA)** of the hypothalamus houses GnRH-neurons that release GnRH in "a pulsatile pattern that in turn stimulates the pulsatile release of two gonadotropins from the anterior pituitary: luteinizing hormone **(LH)** and follicle-stimulating hormone **(FSH).** The activation of the gonadotropins is completed by various signaling pathways dependent on the GnRH pulse frequency (Shalev and Melamed 2020). The onset of pubertal maturation occurs thanks to a steady rhythmic increase in LH and the progression of puberty continues as the LH amount released increases (DiVall and Radovick 2008).

As puberty progresses in humans the ovaries become receptive to the gonadotropins and begin producing estradiol (a form of estrogen). **Estradiol** is the key hormone responsible for the development of breasts, and growth spurt. Accompanying the ovarian production of estradiol, the adrenal glands secrete **androgens** that cause pubic and axillary hair development. Physicians use what is referred to as Tanner staging to determine how individuals are progressing through puberty. This is based on clinical evaluation of pubic hair growth and breast development and provides a simple, ordinal scale that ranges from 1 (prepubertal) to 5 (postpubertal) (Tanner and Whitehouse 1976). **Menarche**, the first period, occurs "after a yearlong rise in daily estradiol output" (DiVall and Radovick, 2008).

An overview of the ovarian cycle and the menstrual cycle

Joanne Richards has been studying the follicular ovarian cycle for over 40 years. Richards (2018) aptly describes the ovarian cycle as “an exquisite, highly orchestrated, and complex developmental process that depends on functional interactions and critical signaling pathways…”. It is characterized by a cyclic pattern of hormonal changes regulated by feedback mechanisms. The ovarian hormones, estradiol, and progesterone are the main modulators of the hypothalamic–pituitary axis. The ovarian cycle is interconnected with the menstrual cycle which is also influenced by the ovarian hormones. Once the ovary is “awakened” during puberty and begins producing estradiol, the process of selection and release of primordial follicles occurs. In humans, the 28-day ovarian cycle is governed by hormones but bear in mind that there is a great deal of variability in cycle length (Rees 1997).

The ovarian cycle has two phases: the follicular and luteal phases. The follicular phase results in the maturation of follicles and ovulation, and the luteal phase involves the development of the corpus luteum (an endocrine structure within the ovary that produces hormones to maintain a uterine environment for potential pregnancy). Concurrently, the menstrual cycle, also controlled by hormones, is responsible for the degeneration and reconstruction of the uterine lining for the successful implantation and support of the embryo. The **menstrual cycle is divided into three phases: menses, the proliferative phase, and the secretory phase.** Menstruation is exhibited in primate mammals as well as a few species of bats and shrews.

Q&A with Dr. Joanne Richards, Ph.D.

Professor in the Department of Molecular and Cellular Biology (MCB) and the Dan L. Duncan Cancer Center at Baylor College of Medicine in Houston, Texas.

Dr. Joanne Richards, Ph.D.

What drew you to becoming a scientist? My life in science came as a surprise, a discovery! It was not a childhood dream; it was not planned. Even today, I do not think of myself as a 'scientist'. What I enjoy and what has captured me is the process of discovery and the challenges of deciphering the secrets of Mother

Nature. Most rewarding have been the unexpected results that have led me down new paths and reminded me that one should always keep an open mind!

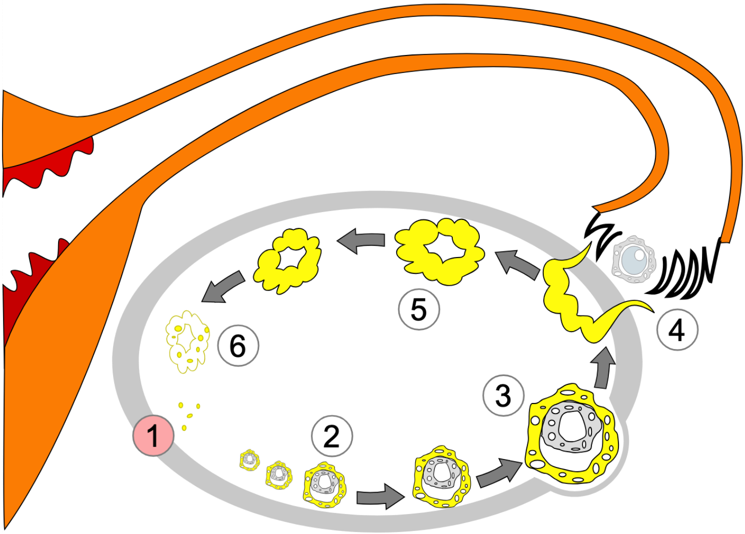
What do you like most about your career? Research is an exacting but exciting career. It is the discovery mode of science and research that is the most fun. It is a detective game! Research in the ovary is particularly intriguing because one studies how ovarian oocytes (eggs) are contained in follicles that are stimulated to grow by hormones coming from the pituitary, FSH, and LH.

How do you see the career path for women in science has changed since you began and what do you hope for the future? There are many more women in science today than when I received my Ph.D. And I think women are contributing significantly in many areas of scientific research. One has only to look at recent women in medicine, biology, and chemistry who have received a Nobel Prize. At scientific meetings, women are no longer a minority but a major force, presidents of societies, panel members on NIH grant reviews, etc. I believe that pattern will continue. Young women just need to decide if science is what they want.

What advice do you have for future women scientists? If you like to discover how things work, you will enjoy a career in science. Scientists in general are not researching to make money. Scientists are trying to understand how things work, to come up with better ways to cure diseases, to identify new compounds to cure diseases, and to identify the basis of diseases to improve human health, prevent diseases, control climate damage, etc. Scientific research is not easy. One has to learn that if an experiment does not work, there is a reason. And if it is not a technical issue then there must be something important to explore. One has to be able to persevere! And to like challenges! But the rewards are realizing what you can and do contribute.

The ovaries and ovarian follicles

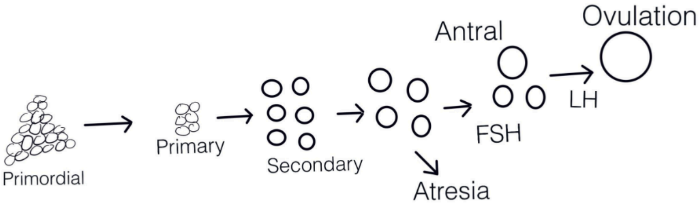
The ovaries are almond-sized (approximately 30 mm long, 25 mm wide, and 15 mm on average) and covered by a thick epithelium. The tissue of the ovaries is divided into two distinct regions: an inner medulla and an outer cortex. The medulla is a loose connective tissue that contains blood vessels, lymph tissue, and nerve cells. Within the cortex reside the ovarian follicles (in different developmental stages, see image below). According to Duncan et al. (2020) follicles are differentiated in size due to differences in their growth phase based on level of maturity: primordial follicles are prenatal, antral follicles are those where a noticeable cavity filled with follicular fluid has developed and Graaffian follicles are mature with the oocyte that is ready to be ovulated. Follicles contain the oocyte and provide an environment for the accumulation of nutrients for future embryogenesis and growth. The oocyte is surrounded by two cell types that work together to produce estrogen: **theca cells and granulosa cells.**



Changes in the ovary during the cycle: 1) menstruation 2) maturing follicle 3) Graafian follicle 4) ovulation 5) corpus luteum 6) disappearance of corpus luteum, image by Shazz, Wikipedia.

Recruitment and differentiation of theca cells

Each mammalian female has an "ovarian reserve" of **primordial follicles**, most of which degenerate through a process known as **atresia**. However, a select few are recruited to complete the final growth phase and get ovulated on a cyclical basis throughout their reproductive lives (see diagram below, modified from Hsueh et al., 2015). By the 20th week of human embryonic development, the number of initial primordial follicles in the fetus is approximately **6 to 7 million**. By puberty, the number has been **reduced** to approximately **400,000-500,000 follicles** (Oktem and Urman 2010). During reproductive life, the continuing growth of primordial and primary follicles into secondary and larger follicles leads to a gradual decrease in the original follicle pool. McGee and Hsueh (2000) provide a detailed description of the recruitment process. From early embryonic development until puberty, some of the primordial follicles become stimulated to initiate growth, whereas the rest of the follicles remain quiescent for months or years. The initially recruited primordial oocytes remain arrested in prophase I of meiosis. The remaining follicles not yet recruited, remain dormant and are probably under some type of constant inhibitory influences to remain that way. Once puberty begins, cyclic recruitment occurs whereby a cohort of follicles is "**rescued**" from atresia known as **antral follicles**. From the cohort, a single follicle becomes the **dominant follicle** as depicted in the diagram below adapted from Hsueh et al (2015).



Select primordial follicles develop to the primary stage through primary and secondary stages before acquiring an antral cavity. The majority undergo atresia. Each cycle select antral follicles supported by FSH compete. A single mature ovum is released after the LH surge. Image created by Jennifer Dever, adapted from Hsueh et al. (2015).

The ovaries experience cyclic changes that involve the maturation and release of eggs as well as the production of progesterone and estrogen. The ovarian cycle is divided into two phases: follicular and luteal.

The follicular phase of the ovarian cycle (days 1-14)

FSH is released from the anterior pituitary

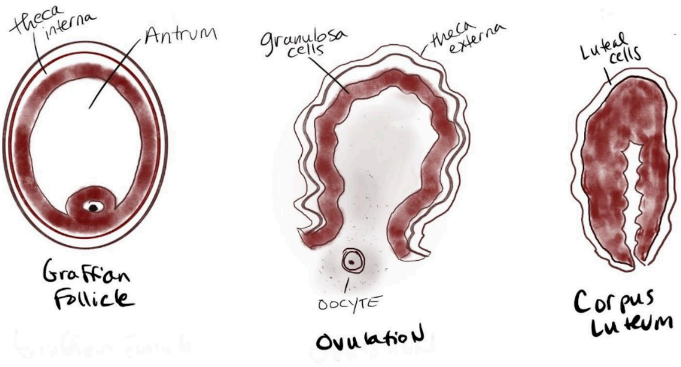
Stimulated by GnRH, FSH is released in a pulsatile fashion from the anterior pituitary. As the level of FSH increases over a 13 to 14-day period, it stimulates the granulosa cells in the cohort of ovarian follicles to synthesize aromatase, which converts androgens produced by the thecal cells to estradiol (one of three different forms of estrogen). FSH also leads to luteinizing hormone (LH) receptor expression on the granulosa cells. Among this group of about 10 antral follicles, a **dominant follicle emerges,** growing faster than the rest of the cohort and producing higher levels of estrogens.

The ovarian cycle experiences negative feedback

As these follicles develop, they start secreting increasing amounts of **inhibin**. Inhibin primarily acts to inhibit the secretion of FSH from the anterior pituitary gland. As inhibin levels rise in response to the developing follicles, it provides negative feedback to the pituitary, reducing the production and release of FSH. Estradiol also plays a role in the negative feedback regulation of FSH and as the follicle grows and estradiol increases it causes FSH to decline. The dominant follicle also produces a higher amount of inhibin, a hormone that also participates in the negative feedback regulation of FSH production. Consequently, the other follicles stop maturing and begin degeneration.

The LH surge and ovulation

At this point of the cycle, a striking surge in LH occurs resulting in positive feedback that causes both a slight surge in FSH and an increase in prostaglandins and proteolytic enzymes. The bump in FSH aids in the final maturation of the dominant follicle. At the same time, the prostaglandins and proteolytic enzymes work to release the dominant follicle (also known as follicular rupture), discharging an ovum (illustrated below). This is ovulation which happens approximately 36 hours after the LH surge and is marked by a notable increase in body temperature. It is thought that ovulation from either ovary happens randomly. An unfertilized egg will eventually disintegrate or dissolve in the uterus. It is also important to know that some cycles are anovulatory meaning that ovulation does not occur.


theca interna
Antrum
Graffian Follicle
granulosa cells
theca externa
OOCYTE
Ovulation
Luteal cells
Corpus Luteum

Once the oocyte is mature, called a Graffian follicle (pictured on left), it is ready for ovulation. The ovary releases the mature oocyte during ovulation (pictured in center) and the corpus luteum remains (pictured on right) secreting progesterone to support a potential pregnancy. Image created by Jennifer Dever.

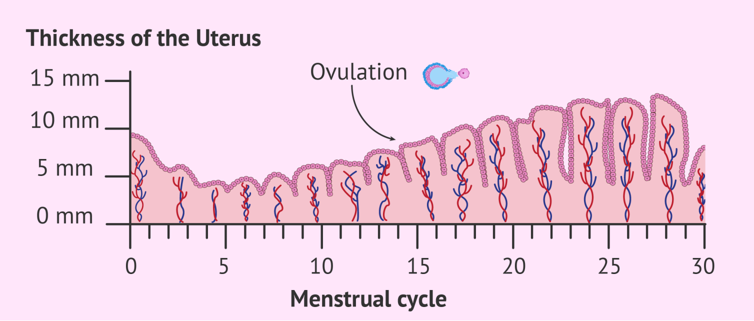
Fertility awareness methods (FAMs) of birth control work to determine the precise time of ovulation to find the relatively fertile and the relatively infertile days in the cycle. The follicular phase length can vary from cycle to cycle therefore monitoring the LH surge and cervical changes is the way to determine when ovulation should occur. The fertility window is referred to as a six-day period with the highest likelihood of conception being approximately five days before ovulation through the day of ovulation. However, Wilcox, Dunson, and Baird (2000) found that conception "during the fertile window is not sufficient to produce pregnancy. Pregnancy depends on the viability of the sperm and egg, the receptivity of the uterus, and other factors that vary widely…"

The luteal phase of the ovarian cycle (days 15-28)

The length of the luteal phase can vary from woman to woman however for each individual it almost always takes the same number of days. After ovulation, the **corpus luteum forms** within the ovary thanks to remaining FSH and LH transforming the remaining parts of the dominant follicle. The corpus luteum is an endocrine structure that produces primarily progesterone and some estrogen. Progesterone encourages the regrowth of the uterine lining in preparation for the implantation of the fertilized egg. It also blocks the release of FSH and LH to prevent any additional follicles from maturing and rupturing. The level of estrogen produced by the corpus luteum increases to a steady level for the next few days and also participates in a negative feedback loop, blocking the release of gonadotropins. If fertilization does not occur the end of the luteal phase is marked by **luteolysis**, or the demise of the corpus luteum. This leads to a sharp decline in progesterone.

The menstrual cycle

The endometrial lining of the uterus has multiple epithelial layers from superficial (top) to basal (bottom) and it experiences changes throughout the cycle (illustrated below). The changes in the endometrial layers characterize the phases of the menstrual cycle and these endometrial changes are the result of hormonal changes. The menstrual cycle is divided into three phases: **menses, proliferative and secretory.** The menstrual cycle is typically represented as beginning on the first day of the menses and ending on the last day before the next menses, with the average length being 28 days (coinciding with the ovarian cycle).



Estrogen released during the follicular phase increases uterine lining (endometrial thickness), and then after ovulation progesterone from the corpus luteum releases progesterone to maintain thickness. If pregnancy does not occur, progesterone levels drop and the functional layer of the endometrium sheds during the menstrual phase. Image from inviTRA.

The menses phase (days 1-5) of the menstrual cycle

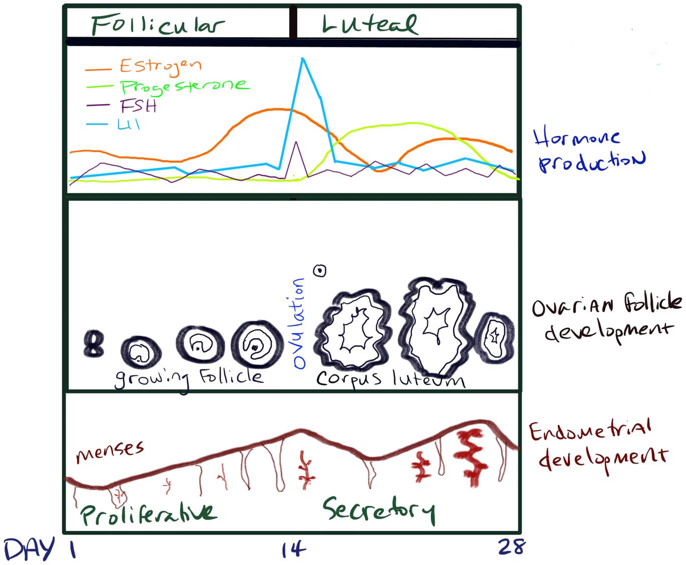
In the absence of pregnancy, a woman experiences menstrual bleeding or what is referred to as "getting her period". This is the menses phase of the cycle which signifies the beginning of the menstrual cycle. The blood is from the production of menstrual fluid composed of endometrial tissue, red blood cells, and proteolytic enzymes and is emitted through the cervix out of the vagina over an average of five days. **Plasmin** released from the endometrial cells prevents clotting. The menstrual fluid is the result of the proteolysis of the endometrial lining and cell death due to the plummeting levels of progesterone (thanks to luteolysis). The significant **decrease in progesterone** also signals to the hypothalamus GnRH neurons to signal to the anterior pituitary, releasing FSH and LH to start the ovarian cycle again. Released by the endometrium, **prostaglandins** play an integral role during menses by causing **vasodilation** which narrows the blood vessels of the endometrium, depriving it of oxygen and promoting shedding and stimulating of the superficial layers and causing contractions in the myometrium (muscular layer of the uterus) to help with the shedding of the endometrial lining. Prostaglandins are also responsible for the side effects of cramping and pain associated with menses. As the endometrial shedding occurs, the ovarian cycle begins and within two days regeneration of the surface endometrial epithelium begins, stimulated by estrogen released from the growing follicles.

The proliferative phase (days 4-14) of the menstrual cycle

To prepare the endometrial lining of the uterus for the potential implantation of a fertilized egg, **estradiol** produced from developing follicles influences the endometrial changes that occur before ovulation. A complete regeneration and restructuring of the endometrial lining with multiple layers and spiral arteries can provide adequate blood flow to the **thickened endometrium**. This enhanced blood flow provides the necessary oxygen and nutrients that would support possible embryo implantation. Estradiol also triggers the development of progesterone receptors in endometrial cells. The cervix also responds to estrogen by producing a mucoid discharge that lowers the acidity of the vagina and makes the environment more hospitable to potential sperm.

The secretory phase (days 15-28) of the menstrual cycle

Further preparation of the endometrium continues thanks to the influence of progesterone produced by the corpus luteum in the ovary. **Progesterone** binds to progesterone receptors on the endometrial cells increasing its vascular supply and stimulation of mucosal secretions. It also increases the surface area within the spiral arteries. Progesterone also decreases and thickens the cervical mucus to inhibit sperm motility. If pregnancy occurs, a fertilized ovum is implanted within the endometrium, and the corpus luteum will persist and maintain the hormone levels. However, if no fertilized ovum is implanted, then the corpus luteum degenerates causing a sharp decline in progesterone and estrogen levels. An overview of the general hormone levels and changes in the ovary and uterus over a 28-day cycle is illustrated below.


Follicular
Luteal
Estrogen
Progesterone
FSH
LH
Hormone production
ovulation
growing Follicle
corpus luteum
Ovarian follicle development
menses
Proliferative
Secretory
Endometrial development
DAY 1
14
28

Rising and falling hormone levels result in the progression of the ovarian and menstrual cycles. Image created by Jennifer Dever.

Problems associated with the cycles

Primary Amenorrhea

If menarche is not reached by age 16 in a young woman who exhibits breast and pubic hair development, she is diagnosed with primary amenorrhea. Klein and Poth (2013) provide a review of the causes of amenorrhea that are attributed to anything that disrupts the onset of the ovarian cycle or prevents the outflow of the shedded endometrial tissue.

Causes of primary amenorrhea

- Outflow tract abnormalities
- Primary ovarian insufficiency
- Hypothalamic or pituitary disorders
- Other endocrine gland disorders
- Chronic disease
- Physiologic (pregnancy) or induced (hormonal contraception)

Secondary Amenorrhea

An absence of menses for greater than three months in females who have had a regular menstrual cycle previously, or an absence of menses for greater than six months in those who have previously had an irregular menstrual cycle is secondary amenorrhea. Klien et al., (2013) note that secondary amenorrhea can often be attributed to polycystic ovary syndrome, problems with the hypothalamus, or premature ovarian failure. Secondary amenorrhea is also associated with low body fat and is common among athletes involved in weight-class and endurance sports (Dadgostar et al. 2009).

Polycystic ovary syndrome

Polycystic ovary syndrome is the formation of multiple cysts within the ovaries due to an imbalance of androgens associated with amenorrhea. Ehrmann (2005) provides a review of this disorder stating that the ovarian theca cells tend to be better at producing testosterone than are normal theca cells in affected women. Furthermore, those with polycystic ovary syndrome also have higher luteinizing hormone pulse frequency which is also associated with greater testosterone production. This is a common disorder affecting up to 10% of all women and evidence indicates a strong genetic component exists.

Abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O)

Anovulation (a lack of ovulation) can be frequent during the first years of the cycle when the HPG axis is immature. Follicular development may start but not complete, nevertheless, estrogens will form and stimulate the uterine lining. Without ovulation, the corpus luteum does not form and progesterone is not released, which serves to stabilize the endometrium until implantation occurs. A lack of progesterone keeps the endometrium in the proliferative phase. This leads to heavy and irregular bleeding known as estrogen breakthrough bleeding. It is also referred to as abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O). The most frequent symptoms are heavy menstrual bleeding, irregular menses, and bleeding between menses (Jones and Sung 2022).

Pre-menstrual syndrome (PMS)

PMS is a combination of physical, emotional, and psychological symptoms that occur in the days or weeks leading up to menstruation. Symptoms can vary widely from mild to severe and may include bloating, breast tenderness, fatigue, irritability, headaches, and mood swings.

Dysmenorrhea

Painful menses are known as dysmenorrhea. Cramping, discomfort, nausea, vomiting, and headaches often accompany menstruation. This menstrual pain can significantly reduce one's quality of life and productivity. Reviewed by Ju, Jones, and Mishra (2014) dysmenorrhea is quite common with studies reporting over 90% of women surveyed experiencing pain during menses. As for the causes of dysmenorrhea, there have been conflicting results across numerous studies. However, a meta-analysis found a positive relationship exists between emotional stress and painful periods as well as family history and there is an inverse relationship between age, oral contraception use, and number of live births.

Menorrhagia

Menorrhagia is abnormally heavy or prolonged bleeding during menses with over 30% of women reporting this problem. It can limit activities and oftentimes leads to anemia (Van Eijkeren et al. 1989). The cause is associated with fibroids (benign endometrial tumors) and prostaglandin disorders (Duckitt and Collins 2012).

Oligomenorrhea

Cycles that last longer than 35 days or those with less than 9 cycles per year are known as oligomenorrhea. Similar to secondary amenorrhea this is often associated with low body fat and therefore experienced commonly by athletes. Oligomenorrhea is not a problem however by itself yet it can be associated with infertility and endometrium proliferation which may result in abnormal endometrial cells (hyperplasia). Endometrial hyperplasia (abnormal endometrial cells associated with abnormal thickening) may lead to endometrial cancer.

Fibroid Tumors

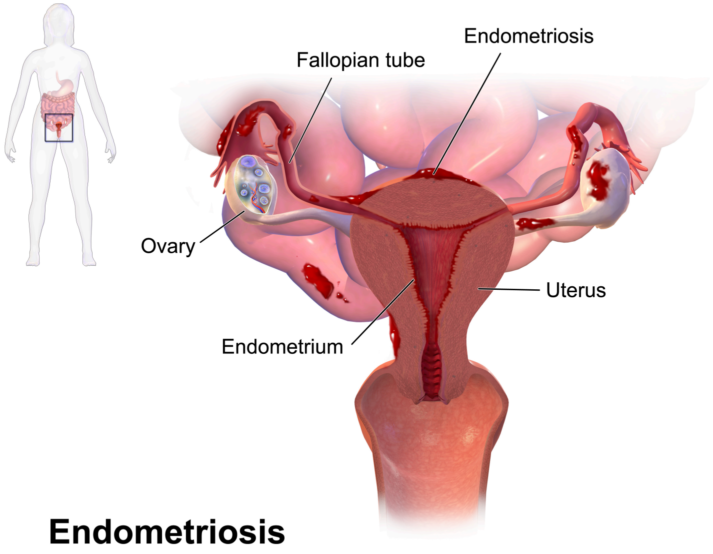
② ①
Prograsp Forceps
Monopolar Curved Scissors
2
Prograsp Forceps
Console 1
3
Fenestrated
Bipolar Forceps
Console 1

Fibroid tumor being removed through laparoscopic surgery.

Fibroid tumors, also known as uterine fibroids or leiomyomas, are noncancerous growths that develop in the muscular wall of the uterus. These growths are composed of smooth muscle tissue and fibrous connective tissue and can vary from small, pea-sized nodules to large, grapefruit-sized masses. Fibroids are quite common and "among 15–54 year-old-women, fibroids account for 29% of gynecologic hospitalizations" ...with "the lifetime risk for fibroids (intended as the cumulative risk of developing a fibroid by age 50) to be nearly 70% in white women and >80% for black women" (Pavone et al. 2018). The image on right is of a fibroid being removed laparoscopically.

Endometriosis

Endometriosis is characterized by the growth of endometrial tissue outside of the uterus. Endometrial lesions likely go through the fallopian tubes and implant on the peritoneal surface or pelvic organs where they become stimulated by estrogen (Vercellini et al. 2014). This results in chronic inflammation every cycle. Chronic pain is a common symptom associated with the overproduction of prostaglandins and cytokines (Howard 2009).


Endometriosis
Fallopian tube
Ovary
Uterus
Endometrium
Endometriosis

Endometrial tissue can grow outside of the uterus causing pain and infertility.

Society and Menstruation

In this modern era, one would expect menstruation to be viewed openly and positively. However, this is not the case for many, and women are still hampered by taboo. Although improvements have been made, as noted by Ramaiyer et al., (2023) we still have a long way to go “in terms of education, research, and cultural acceptance of menstruation.” The World Health Organization (WHO) has asked for the following actions (1) for menstrual health to be framed with the lens of health and human rights as opposed to solely a matter of hygiene; (2) for menstruating individuals to have access to menstruation information, education, and products; and (3) for menstrual health and related support activities be included in relevant government plans and budgets with measured performance (WHO, 2022). A recent article by Mukherjee in the New York Times highlights the many hurdles menstruating women face, ranging from embarrassment to outright exclusion. For too many there is a lack of access to feminine products. As you can imagine, not having pads or tampons directly impacts a woman's quality of life. Even in the United States "**period poverty**" (a lack of access to period products, education, and awareness of menstrual health) is reportedly responsible for 20% of young girls' absence from school, negatively impacting their education and opportunities (Duvuvier et al., 2022). Changes need to be made both locally and globally because all "women have the right to use safe menstrual products during their monthly menses" (Jaafar et al., 2023).

Estrus

Most mammals do not experience menstruation and instead forgo tissue breakdown and bleeding. Furthermore, ovulation is preceded by conspicuous physiological and behavioral changes to signal a female's receptivity to mating. Instead, they go through estrus. In some species, **ovulation occurs spontaneously** in response to hormones, and in others, ovulation is **induced** by mating called "**reflex ovulation**".

The term estrus is derived from the Latin oestrus which means frenzy – referring to the state of a suddenly receptive female experiencing the condition, also known as being in heat. Like menstruation, estrus is also under the regulation of the ovarian cycle and environmental stimuli. For some species, estrus results in outward physiological changes that enable attractiveness and receptiveness to males such as the production of pheromones, genital swelling, and/or reddening. Behavioral changes also may accompany estrus such as vocalization, scent markings, and heightened activity such as the circling of a male observed in wild rabbits (Meyers and Poole 1961). Many species in estrus (e.g. rodents) display a lordosis posture induced by male behavior and increase female receptivity. This behavior is characterized by an elevation of the hind quarters and dorsiflexion of the vertebral column to facilitate penile insertion and aid in fertilization (for review see (Tsukahara, Kanaya, and Yamanouchi 2014).

The four phases of estrus

There are four phases of estrus: **proestrus, estrus, metestrus, and diestrus**. During proestrus, the ovarian follicles start to grow and estrogen begins to rise influencing the endometrial lining. Some animals may experience vaginal secretions. Next during estrus, the dominant follicle emerges and subsequently ruptures releasing the mature ovum. Metestrus is brief and marked by the formation of the corpus luteum after the follicle ruptures. Progesterone levels increase further preparing the uterine lining for implantation. Progesterone also plays a role in the feedback inhibition of estradiol production, resulting in a decline in estrogen. Diestrus is characterized by a continued rise in progesterone by the corpus luteum. In the absence of pregnancy, the corpus luteum regresses, and diestrus ends. The endometrial lining is not shed but rather reorganized for the next cycle. When the reproductive cycle rests the animal is in anestrus.

Typically a seasonal event, estrus is controlled by sunlight exposure and the release of melatonin which regulates the hypothalamic pulse activity of GnRH. Species that experience estrus once a year are monestrus. Seasonally breeding animals active during the fall are known as "short-day breeders" such as deer and elk, those active during the spring and summer are referred to as "long-day breeders" such as horses and hamsters. Some species lack a defined breeding season and experience estrus throughout the year, which is termed continuous polyestrus (e.g. cows). Moreover, the length of the reproductive cycle varies among species and even within species there is variation.

Why do humans and apes undergo menstruation?

As noted above the vast majority of placental mammals do not undergo menstruation therefore the question remains, why?

Currently, there are three main hypotheses regarding the evolution of menstruation which hinge upon the fact that the process known as decidualization occurs. Ng et al. (2020) define **decidualization** as " the functional and morphological changes that occur within the endometrium to form the decidual lining into which the blastocyst implants." Decidualization is essential for proper priming of the endometrium for a successful pregnancy. In preparation for embryo implantation, the endometrial stromal cells undergo significant changes, including enlargement and transformation into decidual cells. These decidual cells are rich in glycogen and lipids and serve as an energy source for the developing embryo allowing for the successful implantation of an embryo.

The hypotheses on menstruation in the great apes

- Humans and apes have a higher level of embryo invasion compared to other mammals. Therefore menstruation serves as a type of protection against excessive invasiveness and is a "nonadaptive result of endometrial spontaneous shedding" (Emera, Romero, and Wagner 2011)

- Menstruation permits embryo selection by the mother (Clarke 1994)
- Menstruation is a side-effect of the fetal–maternal processes that arrest blood supply to the uterine surface upon pregnancy. Progesterone withdrawal causes the constriction of the uterine spiral arterioles, arresting maternal blood flow to the uterine surface, and the cessation of blood supply to the placenta. This is a vital prerequisite for the delivery of the placenta (Thomas 2019)

There are issues with each of the hypotheses but we need to examine the evolutionary underpinnings of menstruation. As Thomas (2019) points out: half of the World's human population menstruates, and the total time experiencing menstruation is at least a quarter of each woman's reproductive years. Menstruation has long been a taboo subject for different religions and cultures, based on ignorance, prejudice, and false information. Yet menstruation is associated with discomfort and health issues for many women. More extensive research to better understand how to manage and alleviate menstrual-related symptoms and conditions is gravely needed.

Think, Pair, Share

There are many gaps in our understanding of the ovarian and menstrual cycles. What are the possible reasons for this?

Every cycle a follicle "wins" and becomes the dominant one that ruptures. Briefly explain this process and develop reasons as to why this process has been selected.

Briefly describe estrogen production during the follicular phase.

How is both positive and negative feedback a part of the cycle regulation?

Describe how the luteal phase of the ovarian cycle and the secretory phase of the menstrual cycle work together to prepare for implantation.

What stimulates estrus and how is this tied into species that have breeding seasons in the spring vs. in the fall?

Deeper Questions

Menstruation evolved independently in shrews and primates. What reasons might there be for selection to result in menstruation over estus and vice versa?

In the literature problems with the menstrual cycle such as premenstrual syndrome and oligomenorrhea are referred to as things women “complain” about. Why might the medical community use the verb “complain” rather than “report” and how does this word impact a physician’s point of view regarding these issues?

If you were designing an oral contraceptive what parts of the ovarian/menstrual cycles would you try to control with it that would be safe and effective?

Why is period poverty still prevalent and how could this be fixed quickly?

Key terms

Amenorrhea
- Anestrus
- Antral follicle
- Atresia
- Corpus luteum
- Decidualization
- Diestrus
- Dysmenorrhea
- Endometrium
- Estradiol
- Estrogen
- Estrus
- Follicle-stimulating hormone
- Gonadotropin-releasing hormone
- Graafian follicle
- Hypothalamus
- Inhibin
- Lordosis

Luteinizing hormone
Luteolysis
Menarche
Menorrhagia
Monestrus
Oligomenorrhea
Oocyte
Ovulation
Pituitary gland
Polycystic ovarian syndrome
Progesterone
Prostaglandins
Reflex ovulation

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Suggested Readings

"In the Flo: Unlock Your Hormonal Advantage and Revolutionize Your Life" by Alisa Vitti – This book explores how understanding and harnessing your hormonal cycle can lead to better health, well-being, and productivity.

"Period Power: Harness Your Hormones and Get Your Cycle Working For You" by Masie Hill – This is a practical blueprint for aligning daily life with the menstrual cycle, to give women a no-nonsense explanation of what the hell happens to their hormones every month and how they can use each phase to its full advantage.

"Cycle Savvy: The Smart Teen's Guide to the Mysteries of Her Body" by Toni Weschler – Designed for teenagers and young adults, this book offers an accessible and informative overview of the menstrual cycle and reproductive health.

"The Menstrual Cycle: Physiology, Reproductive Disorders, and Infertility" by Irina Szmelskyj and Jackie Bernardi – This book provides a detailed exploration of the menstrual cycle from a medical perspective, covering topics related to reproductive disorders and infertility.

"Cycles: The Science of Periods, Why They Matter, and How to Nourish Each Phase" by Amy J. Hammer – Registered nurse Amy Hammer arms you with a strong foundation in physiology and hormonal health, explores historical and socio-cultural aspects of women's health, and reimagines the phases of the menstrual cycle as aligning with the four seasons to provide a detailed guide for living well in your body.

Interesting Podcasts

NPR's Life Kit This is the period talk you should have gotten

PsycheCentral: The menstrual cycle, stigma and mental health

6.

GENDER AND SEXUALITY

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Contrast gender and biological sex
- Identify different terms to describe gender identity
- Explain why gender and sexuality are often conflated but should be considered separately
- Discuss sexual orientation and its connection to identity
- Describe the connection between the hormones, the brain, and sexuality
- Describe the sexual response cycle in females and discuss the hallmarks of each stage
- Define sexual dysfunction in women and recall some of its causes

A traditional view of gender and biological sex

Around the 20th week of pregnancy, many expectant parents in the United States decide to hold a "gender reveal party". A quick Google search of "gender reveal party ideas" produces a myriad of things one can do such as hiring a baker to fill a cake with pink or blue icing, filling an opaque balloon with pink or blue confetti, or filling a large cardboard box with helium-filled pink or blue balloons that will float out when opened. Notice they involve a binary code (pink or blue) for the big reveal. These parties reassert the standard idea of binary gender, girls are pink and boys are blue (Gieseler 2018). In the United States, this code can be traced back to Alcott's (1868) Little Women: where "Amy ties a pink bow and a blue bow on Meg's twins Daisy and Demi so people will know the difference between the girl and the boy", (Frassanito and Pettorini 2008). However, it did not stick until the 1940s when children's clothing was mass-produced rather than home-made, and manufacturers and retailers understood how they could sell twice as many goods with a binary code, thereby reducing gender-neutral options (Paoletti 2012). Over the next 40 years trends shifted but the pink-girl-blue-boy code became the norm from the 80s onward. Nevertheless, as straightforward as a pink-blue code may seem, it is misleading because people falsely assume that there are only two genders and that an infant's gender identity is the same as their biological sex.

Separating gender from biological sex

Defining biological sex

Biological sex is related to gender but they are two very different things. To understand sex we must first tease the concept of a person's gender apart from a person's biological sex. As noted in the chapter on the *Evolution of Sex*, if we stick to sexually reproducing multi-celled organisms, biological sex can be fundamentally defined by **anisogamy**, with females producing large eggs and males producing small sperm. Using this simple definition of biological sex allows a clear distinction between individuals of the female sex and those of the male sex. This helps us to understand how differences in anatomy, physiology, and behavior between sexes would arise and persist (Parker 2014).

Why not just use sex chromosomes to define sex? When biological sex is defined by the presence/absence of sex chromosomes with those having XX chromosomes versus an XY to define the female and male respectively, then key groups are left (i.e. crocodilians or turtles that exhibit environmental sex determination). This definition also excludes birds and some insects whose females exhibit heterogametic sex (ZW) chromosomes. Furthermore, nearly half of all plant species lack sex chromosomes altogether. When we consider the role of genes involved in sex determination it is apparent that **key genes are important for determining a particular sex but not in defining it** (see the chapter on the *Genetics of Sex*).

Furthermore, female and male-associated traits have complex genetic architectures, meaning multiple genes interact with one another and the environment to produce them. So, although the fundamental anisogamy-definition of biological sex is simple, the actual realization of biological sex is still quite complicated. Anisogamy-defined sex is useful because it spans different groups of sexually reproducing organisms without constraint and allows for the flexibility of diversity observed in disparate groups.

Defining gender

Gender is a deeply personal and psychological aspect of a person's identity(**identity is who a person thinks they are).** Gender is multidimensional, "shaped by individual characteristics, family dynamics, historical factors, and social and political context" (Tatum 2000). A person's gender identity determines how people view themselves in the cultural normative context (Wood and Eagly 2009), and "provides an important basis for their interactions with others" (Steensma et al. 2013). Therefore a person's gender is separate from a person's sex because gender is how a person feels, what they perceive about their biological sex, and how they want to behave relative to their biological sex.

Social ideas about gender are connected to biological sex because femininity and masculinity (attributes regarded as characteristic of women and men) are directly impacted by sex hormones. Many feel that gender and sex are "mutually constitutive categories that must be considered in tandem" (Schudson, Beischel, and van Anders 2019). Adding to the confusion is the fact that in the United States (as is the case with most countries), we are assigned a biological sex (female or male), at birth based on our external genitalia. It is automatically assumed that this assignment extends to one's gender.

However, as Bittner and Goodyear-Grant (2017) note, "(1) sex and gender are distinct, even if they overlap and (2) that gender is at least partly explained by socialization, even if it is also biologically influenced". Gender is comprised of different components as follows: a) physiological/ bodily aspects (sex); (b) gender identity or self-defined gender; (c) legal gender; and (d) social gender in terms of norm-related behaviors and gender expressions (Lindqvist, Gustafsson Sendén, and Renström 2021). Each of these components can change over a lifetime. Moreover, because one's gender identity can change over time, and can be fluid, strict binary assignment disregards whether or not our personal-held gender identification matches that “assignment”. Distress can result from “incongruence between experienced/ expressed gender and assigned gender” known as gender dysphoria (Steensma et al. 2013).

When considering gender identity **we must be respectful and inclusive** with our language and promote an understanding of the diversity of human experiences. Gender identities can vary beyond the binary categories of male and female. The following terminology is used by some to describe gender identities (Rioux et al. 2022).

Commonly Used Gender Identity Terms

Agender: not having a gender.

Bigender/Trigender/Pangender: individuals who feel they are two, three, or all genders. They may shift between these genders or be all of them at the same time.

Boi: a female-bodied individual who expresses or presents themselves in a culturally/ stereotypically masculine, particularly boyish way.

Butch: a masculine gender expression which can be used to describe people of any gender.

Cisgender: a term used to describe an individual whose gender identity aligns with the one typically associated with the sex assigned to them at birth.

Dead name: the birth name of somebody who has changed their name. Most commonly attributed to transgender individuals, but can be attributed to anyone who has changed their name.

Femme: a feminine gender expression used to describe people of any gender.

Gender nonconforming: a person who views their gender identity as one of many possible genders beyond strictly female or male.

Gender diverse: an umbrella term for people who expand notions of gender expression and identity beyond societal gender norms.

Gender expression: the way a person publicly expresses their gender to others through appearance and mannerisms (e.g., the way one dresses, talks, acts, moves).

Gender fluid: when a person does not identify solely as male or female, and their gender identity changes over time.

Intergender: An individual who feels their gender identity is between man and woman, both man and woman, or outside of the binary of man and woman.

Non-binary: when a person may identify as being both a man and woman, somewhere in between, or as falling completely outside these categories. Non-binary can also be used as an umbrella term encompassing identities such as agender by gender genderqueer or gender fluid.

Transgender: an umbrella term for people whose gender identity and or expression is different from cultural expectations based on the sex they were assigned at birth.

Transition: a broad definition is the process transgender people may go through to become comfortable in terms of their gender.

Sensitivity about gender is needed

Whereas sex is the result of billions of years of evolution gender is not, and in this modern era humans should be free to express their gender identity how best fits them. Yet, that is often not the case. Gender-diverse individuals face "substantial discrimination, prejudice, and bias, resulting in social inequalities and stigma" (Drabish and Theeke, 2021). As Tatum (2000) points out those who consider themselves members of the dominant social group take their identity for granted, "their inner experience and outer circumstance are in harmony with one another, and the image reflected by others is similar to the image within". Not everyone experiences this advantage. The struggle for trans people in particular is real, with several research studies documenting that 40% or more of those identifying as trans have attempted suicide at least once in their lifetime (Dickey and Budge 2020). In a recent review by Chan et al.,(2023) it was reported that discrimination and inequality of healthcare for transgender athletes was noted in over a third of those surveyed and that they had significantly higher rates of suicide than cis-gendered athletes.

Furthermore, respecting pronouns (she/him/they) is gender-affirming and a failure to do so is a form of misgendering and can be damaging to the individual (Yarbrough 2018). Always "listen for and respect a person's self-identified terminology" (Human Rights Campaign website) so that people may feel empowered and seen. Sensitivity regarding gender is necessary to create a more inclusive, equitable, and respectful society. It acknowledges the diversity of gender identities, promotes the well-being of individuals, and helps protect the rights of those who do not conform to traditional gender norms.

Separating gender from sexuality and sexual orientation

Human sexuality is complex and comprises much more than sexual acts alone. It is a combination of attraction, thoughts, desires, fantasies, and sexual roles. According to the American Psychological Association (2023), an individual's sexuality encompasses emotional, romantic and/or sexual attraction to another. Similar to gender, sexuality also refers to an individual's sense of personal and social identity but it is based on "attractions, related behaviors, and membership in a community of others who share those attractions and behaviors."

The terms sexual identity and sexual orientation are often used interchangeably however Moser (2016) clearly defines sexual identity as "how individuals define themselves sexually. It may or may not describe their actual sexual behavior, fantasy content, or to which sexual stimuli they respond". In comparison, sexual orientation is defined as a type of romantic and/or sexual interest toward persons of the same gender or biological sex, persons of the other gender or biological sex (heterosexual), or both genders/biological sex. Sexual orientation is flexible, complex, and multifaceted and reflects the diversity of sexual, affectional, and erotic attractions and love toward persons of the same gender, another gender, or both genders (Garnets 2002).

Because sexual orientation is part of one's identity and sexual preferences it is directly connected to both sex and gender and the two are often automatically combined. Part of the conflation of sexuality and gender comes from the fact that commonly used sexual orientation identity terms are based on a gender binary. Everyone's experiences of sexuality are unique and it's crucial to support individuals, embracing and expressing their authentic selves, free from stereotypes and prejudices.

Commonly Used Sexual Orientation Terminology

Heterosexual or straight (female-male preference)

Homosexual (same-sex preference) – Lesbian (female-female preference) and Gay (male-male preference)

Bisexual (both male and female preference)

Asexual (preference for neither) – a person who does not experience sexual attraction.

Ace – umbrella term to describe a lack of, varying, or occasional experiences of sexual attraction.

Pansexual – a person who is sexually, emotionally, romantically, or spiritually attracted to others, regardless of biological sex, gender expression (of masculine or feminine characteristics), or sexual orientation" (Rice, 2015).

Queer – once used as a slur this term has been reclaimed by the LQBT community it is "currently used to acknowledge the non-normative" … queer is used as an "umbrella term to describe the non-heterosexual" (Panfil 2020).

Questioning – a term used to describe those who are in a process of discovery and exploration about their sexual orientation, gender identity, gender expression, or a combination thereof.

LGBTQ+ – The acronym for lesbian, gay, bi, trans, queer, questioning and ace.

According to Morandini, Dacosta, and Dar-Nimrod (2021), there is a "problem with viewing sexual orientation as existing in binary gay/straight categories…because it leads gay/lesbian individuals to be seen as more fundamentally different".

Furthermore, it is not reflective of many people's experiences. Kinsey, Pomeroy, and Martin (1948) first studied sexuality in men and found evidence of sexuality being more of a continuum rather than individuals adhering to rigid completely heterosexual or homosexual preferences. Moreover, sexuality can be fluid. Ventriglio and Bhugra (2019) define sexual fluidity as "changes in sexual identity and sexuality as a result of internal and external factors." Thelwall et al. (2023) report academic researchers use several different terminologies, with "this plurality probably reflecting differing needs."

The brain, genes, and sexuality

Sexuality and sexual orientation development involve complex interactions among a network of distinct endogenous and exogenous factors. The heart is a vital organ; thus, historic metaphorical language has treated it as the source of emotions, desire, and wisdom. However, neuroscience has helped us to understand that feelings are a neurological mechanism impacted by hormones and connected to the brain (van Wingen et al. 2011). According to Bakker (2021), several morphological and neurochemical sex differences are induced by hormones specifically during the perinatal period "...are thought to be at the basis of sex differences in the control of reproductive functions".

During early embryonic development, the fetus is exposed to testosterone and estrogens that bind to steroid hormone receptors in the brain (McCarthy et al. 2009). Margaret McCarthy is a leading neuroscientist who has made significant discoveries related to gender differences and the brain. Her seminal research focuses on the influence of steroid hormones on the developing brain with a special emphasis on understanding the cellular mechanisms that establish sex differences.

Q&A with Dr. Margaret M. McCarthy Ph.D.

Director, University of Maryland – Medicine Institute of Neuroscience Discovery

Dr. Margaret McCarthy, Ph.D.

What drew you to studying the brain and specifically the sexual dimorphism of the brain? I started with a keen interest in animal behavior from the perspective of evolutionary biology (most of my colleagues started as psychologists), and that naturally led to the brain which at the time was truly the last frontier in that we knew so little. I always remind students that the discipline of neuroscience, if you base it on the first meeting of the Society for Neuroscience, is only a bit over 50 years old whereas chemistry and physics are hundreds of years old. As I became more interested in how evolution acted on organisms via behavioral expression this naturally led to reproduction as it is directly tied to fitness. During my master's thesis, I studied maternal behavior in mice as well as infanticidal behavior committed by both males and females to enhance their reproductive fitness, this was a paradigm shift from the view that infanticide was a pathology created by domestication in the laboratory. From there I extended my work to mating behavior during my PhD and postdoc. I was always fascinated by the Sexually Dimorphic Nucleus of the Preoptic Area (SDN) as an anatomical structure that could mediate sex differences in behavior and the last experiment I did as a postdoc involved using antisense oligonucleotides to manipulate its size. I then vowed if I was lucky enough to get my very own lab I would commit to studying how sex differences in the brain form at the time they are established as a means to discover novel mechanisms.

What have you enjoyed most about your research? It would be hard to pinpoint any one thing. From the scientific perspective, I have enjoyed that we have generated fundamental new knowledge about how the brain is built, and this was achieved by comparing males and females as they develop, I liken it to using sex as a contrast agent. Since we are one of only a few labs that study sex differences as they happen there has been a lot of low-hanging fruit and so we have made some surprising discoveries of roles for the immune system and inflammatory signaling molecules that are not related to illness, just normal brain development. Outside of science, I have enjoyed the incredible travel I have been able to do because I'm a scientist, I have been to places I never would have gone if not for the invitation and have made friends all over the world, including China, Japan, Brazil, Mexico, Canada, Iran, Slovenia, Italy, Germany, France, Spain and Ireland, I'm sure there are more I am forgetting. Lastly, because I have been successful in research I have also been able to influence the research enterprise through leadership positions both in scientific societies, as a reviewer and editor of journals, and as a director of graduate education and chair of a department at my home institution. Not only does this let me participate in deciding the direction of research, but I also get to promote the careers of trainees, both my own and others. Nothing is more fun than the day a student defends their thesis or a postdoc gets a job, these are fulfilling moments.

What do you find most challenging about your career? Again so many things. One is the work never ends and the criticism never stops. It never gets easier to read the critiques of your manuscript or grant proposal, especially when it is anonymous and you often do not get a chance to reply, just a REJECT. It is hard to see students go through this as well but it is a big part of the discipline and so you have to be able to deal with it. As to the work never stopping, not only is there always more to do, but there is always someone who is doing more and better than you. I know scientists are not supposed to be competitive but of course we are. Sometimes I think I would be happier as an organic berry farmer.

What advice do you have for future women scientists? This is the hardest to answer as there is no one panacea to the challenges women face. It has been disheartening to see how many women start out and are so enthusiastic and then leak out of the pipeline. The pandemic devastated the women in my lab and seemed to energize the men. Of course, childcare is one of the biggest challenges but so is the relentless stress so my, somewhat cheesy, advice is to remember that science is a fast-moving train and your job is to stay on the train every day. Some days you will be hanging onto the caboose by your fingertips, but other days you will be the engineer, so just stay on cause once the train leaves the station without you, it is gone, and you can't get back on (overly dramatic I know). In some ways this is freeing, there is no deciding whether to take a few years off and raise the kids till the first grade or go part-time, you have to commit fully and so the lack of choices is a benefit. I never felt guilty about working when raising my kids, despite my mother-in-law's best efforts. The benefits of academic science are that you are not punching a clock and so outside of teaching you have enormous day-to-day flexibility to do things like take the kids to the doctor, go on field trips, etc. and this is a real plus. Last bit of advice, try not to take anything personally, it is about the science, and even if it is not tell yourself it is, unless there is clear evidence of bias or harassment, in that case, fight like hell.

What role do hormones play?

Rodent studies have provided some insight into the role hormones play in sexually dimorphic behavior. For instance, in hamsters, the amygdala has many androgen receptors, and amygdala-dependent behaviors (important for learning) are influenced by testosterone (Wood and Newman 1995). Hormone activity in the brain of adult mice is essential for reproductive behavior. The role of nuclear **ER*α* estrogen receptors** in the reproductive behavior of female mice was demonstrated by Ogawa et al. (1998) who created knock-out mice lacking these receptors and observed that these females lacked sexual receptivity. In humans, sex-specific differences in the strength of binding of ERα have been observed with females having significantly greater activity in their **ventromedial nucleus** (VMN), a specific nucleus within the hypothalamus (Liu and Shi 2015).

Additionally, adult female and male brains have a sexually dimorphic region within the hypothalamus called the sexually dimorphic nucleus of the preoptic area **(SDN-POA)** (Hofman and Swaab 1989). It is hypothesized that this region along with the third interstitial nucleus of the anterior hypothalamus (INAH-3) "may be partially processing sex stimuli associated with basic attractions to others" (Wang, Wu, and Sun 2019). High concentrations of both estradiol and testosterone have been observed in the human female hypothalamus and POA (Bixo et al. 1995). For both women and men, **testosterone** has an activating effect on sexual interest (also known as **libido**) (Davis and Tran 2001).

In addition to circulating blood hormone levels impacting gene expression, other environmental factors trigger epigenetic control of genes involved in receptivity. Multiple genes on several chromosomes are involved. A recent genome-wide association study (GWAS) reported by Ganna et al. (2019), revealed that numerous loci underlie sexual behavior in both sexes and found five autosomal loci to be significantly associated with same-sex sexual behavior. Not only does the presence of sex-specific genes matter, but how the genes are regulated also helps understand sex-dependent sensitivity to stimuli (Forger 2016). Research is still needed to help us better understand this complex topic, specifically on the epigenetic control of gene expression and the impact of environmental factors on the establishment of sexuality.

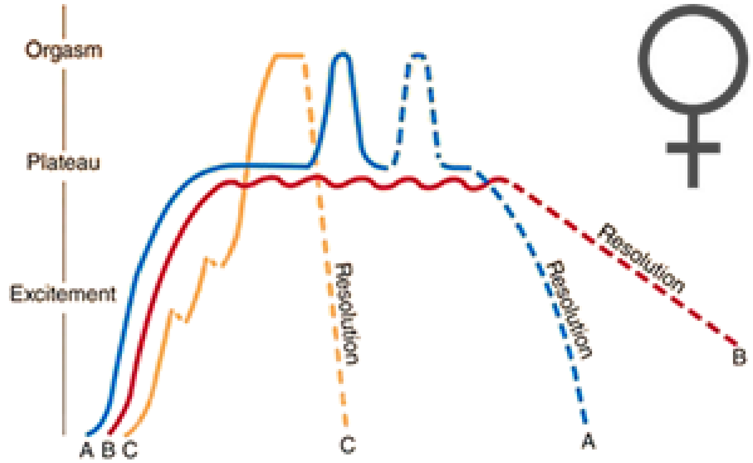
The female sexual response

When it comes to sexual activity humans are among just a handful of animals that do not limit sexual activity to reproduction. Like humans, bonobos, white-faced capuchins, and dolphins have been observed to engage in "social sex" that involves mating beyond the breeding season, homosexual activity, and mating with other species (Manson, Perry, and Parish 1997; Markowitz, Markowitz, and Morton 2010). Unlocking the complex psychology and physiology of the sexual behavior of humans is an ongoing endeavor. Two instrumental research studies that laid the foundation of this field and challenged societal norms were led by Alfred Kinsey and William Masters & Virgina Johnson.

Alfred Kinsey was one of the first scientists to extensively study sexual behavior in women. He and his associates surveyed and interviewed thousands of individuals from across the United States, compiling a comprehensive dataset published in his book "Sexual Behavior in the Human Female" (1953) (a follow-up to his first study on male sexual behavior). One ground-breaking area that Kinsey investigated, in particular, was the female orgasm where he dispelled myths and misconceptions surrounding women's ability to experience pleasure and orgasm, arguing that women and men shared the physiological capacity to respond to sexual stimulation. In 1966 another revolutionary study that delved more deeply into the physiological side of sexual behavior was published in the book "Human Sexual Response" by **Masters and Johnson**. This landmark work fundamentally changed how society and scientists approached the study and understanding of the human sexual response (Gerhard 2000).

Masters and Johnson (1966) directly observed women and men engaging in masturbation and sexual activity, enabling them to measure the physical and physiological responses of participants, including heart rate, blood pressure, skin tone changes, muscle tension, and respiratory rates. They found that a woman's clitoris is the main erogenic zone (an area that can produce sexual arousal when stimulated). They also discovered that the main difference between women and men was a woman's capacity for multiple orgasms, which men lack.

Masters and Johnson identified a pattern shared among both women and men which they called the **sexual response cycle**, divided into four successive phases (**EPOR**): Excitement, Plateau, Orgasm, and Resolution, depicted in the image below. During the response cycle, two key physiological mechanisms were observed (both in genitalia and throughout the body): vasocongestion (increased blood flow into the organs so that the tissues become engorged and usually undergo a color change) and myotonia (increased muscular tension that occurs both voluntarily and involuntarily). The following describes the hallmarks of each phase however bear in mind that this cycle represents a composite of potential physiological responses and varies greatly from person to person. There are also important psychological elements to each stage.



The female EPOR response cycle (Masters & Johnson). Women are capable of multiple orgasms as indicated by the blue dashed line.

Hallmarks of the EPOR response cycle

Excitement phase – during this phase, physiological and psychological changes happen when an individual becomes sexually aroused in response to sexual stimuli or desire. Most women reported clitoral stimulation alone established the excitement phase. The following are hallmarks of the excitement phase:

- Vasocongestion: Blood flow increases to the genital area, leading to engorgement of the swelling of the clitoris as the corpora cavernosa becomes engorged with blood. The uterus becomes engorged and moves upward. The vaginal walls expand and transducate from the vaginal walls, increasing vaginal lubrication. The labia minora swell and their color darkens.
- Nipple Eection: The areola enlarges and swells, and the breast size increases.
- Increased Heart Rate: The heart rate increases due to heightened arousal and the release of adrenaline.
- Flushed Skin: Increased blood flow can cause the skin to appear flushed or reddened, particularly in the neck area.
- Increased Respiration: Breathing becomes more rapid and shallow, partly due to increased oxygen demand during arousal.
- Myotonia: Muscles throughout the body, including those in the genital area, may become tense and contract as a result of increased blood flow and arousal.
- Bartholin's Gland Secretion: small amounts of mucoid material may be excreted late in the excitement phase.

Plateau phase – during this phase, "sexual tensions are intensified and the duration is dependent upon the stimuli employed combined with the individual drove for culmination”. The following are hallmarks of the plateau phase:

- Vulvar Erection: the bulbs become swollen, and the uterus is further elevated.
- Clitoris Retraction: the body and glans of the clitoris retract from their non-stimulated overhanging position and withdraw deep under the prepuce carrying the labia minora and the suspensory ligament along toward the pubic synthesis; although no longer visible, the clitoris is still responsive to stimulation.
- Sex Flush Spreads: the labia majora continues to show more color changes and there is further swelling of the areola and the flush spreads over the breasts and the shoulders (varying among women).
- Myotonia Continues: further tightening of the muscles occurs.
- Increased Heart Rate: further elevation in heart rate occurs

Orgasm phase – This is the culmination of sexual arousal. During this phase (limited to a few seconds), the vasocongestion and myotonia are released after an involuntary climax is reached. There is great variability in the intensity and duration of the orgasmic experience. Sherlock et al. (2016) surveyed women and found that orgasm variation is contingent upon sexual skill. The following are hallmarks of the orgasm phase:

- Rhythmic Contractions: the muscles that make up the vaginal wall and vulva undergo contractions. This can also happen in the anal sphincter. The intensity and number of contractions vary.
- Sex Flush Peak: flush reaches peak intensity.
- Total-Body Involvement: some voluntary muscular control is lost as the involuntary contraction of multiple muscle groups occurs (e.g. pelvic floor muscles; deep abdominal muscles).

Resolution phase – orgasm is directly followed by an involuntary period of tension loss returning the individual to an unstimulated state. “Women have the response potential of returning to another orgasmic experience from any point in the resolution phase”. The following are hallmarks of the resolution phase:

- Blood Drains: blood is released and drains out of engorged tissues.
- Skin Color Returns: the coloration of skin returns to pre-excitement state, sex flush disappears.

Individuals may experience variations in the intensity and duration of each phase and the sexual response cycle is not always linear. People can move back and forth between phases or skip certain phases depending on the circumstances. Furthermore, the EPOR model is simply a model to provide a point of reference, not a rule, and varies among individuals. There is also a notable difference between women and men. For example, a woman can experience multiple orgasms during the O phase before resolution (Masters and Johnson, 1966).

The EPOR model has been refined over the years with different models allowing for increased complexity (reviewed by Wylie and Mimoun, 2009). Kaplan (1974) proposed a three-phase model composed of desire, arousal, and orgasm whereas Basson proposed a circular sexual response pattern (2001). More recently, the sexual tipping point (STP) model (Perelman, 2009) allows for greater complexity and variability among women and states that sex is both mental and physical and that the mind and body both inhibit and excite sexual response. The specific "tipping point" for a sexual response is determined by multiple factors at any given moment or circumstance.

Female sexual dysfunction

Women may experience difficulties during one or more stages of the sexual response cycle and if these cause distress or prevent the individual from feeling satisfied with the sexual activity they are classified as sexual dysfunction (Chen et al. 2013). The prevalence of sexual dysfunction in women appears to be high. Hayes et al. (2006) analyzed data from multiple studies and found that 64% of women reported having sexual difficulty with 62-89% persisting for at least several months. They also found a striking pattern across different studies: reports of sexual desire difficulties are the most common, followed by orgasm difficulties (known as anorgasmia), arousal difficulties, and pain associated with sexual activity (referred to as dyspareunia).

What causes sexual dysfunction in women?

Faubion and Rullo (2015) provide a review of the topic noting that the causes of female sexual dysfunction are multifaceted, including biological, psychological, and sociocultural factors. Problems with desire can stem from medical issues that directly or indirectly impact function such as vascular disease, cancer, bladder problems, and neuromuscular disorders. Vaginismus, a condition that causes spasms from fear of penetration, can result in painful sex. Antidepressants that have serotonin-enhancing abilities can have an inhibitory effect on sexual function, impacting desire, excitement, and orgasm. Hormonal changes throughout one's life may hinder sexual function. Testosterone levels gradually decline as women age and menopause is marked by a sharp decline in estrogen levels that directly impacts vaginal lubrication.

Treatment for sexual dysfunction

The first step to treatment involves identifying underlying issues. Therefore a comprehensive medical and psychosocial history is highly recommended and there are multiple treatment modalities depending on the specific issue (Basson et al. 2010). The treatment may be as simple as using a safe over-the-counter water-based vaginal lubricant. Or it may require prescription medication. Two drugs to treat low sexual desire in premenopausal women have been recently given FDA approval: fibanserin (Addyi) a daily pill, and bremelanotide (Vyleesi) an injectable that can be used up to eight times per month.

Sexuality is a normal and healthy part of the human experience. Individuals must have the autonomy and support to explore and understand their sexuality in a way that is safe, consensual, and fulfilling. Open communication, education, and a non-judgmental approach to one's own and others' sexuality can help demystify and navigate the complexities of human sexual experience. We must also keep in mind that **there is no "right" way to be sexual;** what matters most is that individuals have a healthy and satisfying sexual experience that aligns with their values and desires.

Think, Pair, Share

In your own words describe the difference between gender and biological sex.

Drabish and Theeke (2021) report transgender people experience “inequalities and stigma…which negatively impacts health outcomes and changes in the psychological and physical health of transgender people”. Why would this be happening in a healthcare setting where physicians are supposed to adhere to the Hippocratic oath which states: *I will keep patients from harm and injustice*?

We discussed the physical and physiological changes that women experience during the four stages of the sexual response cycle. What psychological changes might a woman experience during each stage?

What do you think sexual dysfunction is for men, for women? How common is it for women and why might people not discuss it as often as they do for men?

Deeper Questions

How does the profound disconnection between one's inner sense of self and the external perceptions of their gender in gender dysphoria challenge our understanding of identity, authenticity, and the intricate interplay between the physical body, social constructs, and the essence of who we truly are?

It is hypothesized that levels of particular sex hormones in the bloodstream might increase or decrease a person's level of sexual desire so would a transdermal testosterone and estrogen patch alone increase libido?

Women have a greater capacity for orgasm yet they seem to have more difficulty experiencing orgasm than men. Why?

Key Terms

Biological sex

Bisexual

Cisgender

Gender

Gender diverse

Gender nonconforming

Heterosexual

Homosexual
Myotonia
Nonbinary
Nucleus of the preoptic area
Pansexual
Queer
Sexual response cycle
Sexual dysfunction
Transgender
Vaginismus
Ventromedial nuclei
Vasocongestion

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Suggested Reading

"The Other Big Bang: The Story of Sex and Its Human Legacy" by Eric Haag – Haag provides a thoughtful examination of the evolution for a better understanding of modern society's notion of gender to help bend the arc of history toward gender equality.

"Gender Trouble: Feminism and the Subversion of Identity" by Judith Butler – Judith Butler's influential work explores the performative nature of gender and challenges traditional notions of identity and sexuality.

"Sex, Time, and Power: How Women's Sexuality Shaped Human Evolution" by Leonard Shlain – Shlain presents a unique perspective on the evolution of sex by examining how women's sexual biology and reproductive capabilities have influenced human history and culture.

"The Second Sex" by Simone de Beauvoir – Simone de Beauvoir's classic feminist text delves into the construction of femininity and the historical oppression of women, providing a foundational perspective on gender.

"Whipping Girl: A Transsexual Woman on Sexism and the Scapegoating of Femininity" by Julia Serano – Julia Serano discusses the intersection of gender, sexuality, and feminism, with a focus on the experiences of trans women and the stereotypes they face.

"The Straight Mind and Other Essays" by Monique Wittig – Monique Wittig's essays challenge conventional notions of heterosexuality and the construction of gender, offering a queer feminist perspective.

"Queer: A Graphic History" by Meg-John Barker and Julia Scheele – This graphic novel provides a concise overview of queer theory, exploring key concepts related to gender and sexuality in an accessible format.

"Sexual Fluidity: Understanding Women's Love and Desire" by Lisa M. Diamond – Lisa Diamond's research-based book explores the concept of sexual fluidity in women, challenging rigid definitions of sexual orientation.

"The Invisible Orientation: An Introduction to Asexuality" by Julie Sondra Decker – This book provides an introduction to asexuality and the experiences of individuals who do not experience sexual attraction.

"The ABC's of LGBT+" by Ashley Mardell – Aimed at young adults and newcomers to LGBTQ+ topics, this book offers an accessible and inclusive introduction to gender and sexuality diversity.

"Gender and Our Brains: How New Neuroscience Explodes the Myths of the Male and Female Minds" by Gina Rippon – Gina Rippon discusses recent findings in neuroscience that challenge traditional ideas about gender differences in the brain, including the genetic factors that influence brain development.

"The Sexual Brain" by Simon LeVay – Simon LeVay, a neuroscientist, explores the biological basis of sexual orientation and how genetics and brain structure can influence sexual identity.

Interesting Podcast

Hidden Brain: The Edge of Gender

7.

CONTRACEPTION

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Recall the key reasons that access to contraception is crucial for women
- Identify the reasons for unmet contraceptive needs
- Discuss Margaret Sanger's involvement in the development of the birth control pill
- List the factors a woman should consider when deciding on a particular contraceptive method
- Discuss why there is no such thing as a perfect contraceptive method
- Compare and contrast the different methods of contraception
- Explain the difference between "perfect-use" and "typical-use" effectivity of methods
- Identify the different types of hormonal contraception and explain how they work

Unmet contraceptive needs represent a public health and social issue

The Oxford English dictionary defines contraception as the act of intentionally preventing pregnancy by employing devices, practices, medications, or surgery. It is also known as birth control. As noted in the 9th edition of the seminal text Our Bodies Ourselves written by the Boston Women's Health Book Collective (2011) "our ability to prevent or delay pregnancy is fundamental to our ability to choose how we live our lives." Access to contraception is crucial for women for many reasons and it is elemental to promoting empowerment and health. Why is it so crucial for women to access contraception?

Reasons why access to contraception is important for women

- Reproductive choice: Contraception provides women with the ability to plan their pregnancies and avoid unintended pregnancies.
- Educational and career opportunities: Contraception allows women to plan their

lives so they may pursue higher education and professional career growth.

- Economic empowerment: By planning pregnancies women can improve their ability to manage resources and lessen the number of dependents to support until a time when they are more able.
- Health benefits: Contraception lowers mortality rates and some methods provide non-contraceptive health benefits such as controlling menstruation symptoms.
- Gender equity: Contraception provides autonomy and agency for women by empowering them to control their own reproductive lives.
- Poverty reduction: Contraception helps break the cycle of poverty by allowing women to control their family size. They are also more likely to take advantage of opportunities for themselves and their families.

A brief history of contraception

The first Western contraceptive measures were described in 3000 BCE as male penile sheaths (early condoms) made from animal bladders and intestines and in ancient China oil-lubed sheaths made from silk were used. In Japan, these early condoms were crafted from tortoise shells known as the Kabuta-Gata (Khan et al. 2013). While these primitive barriers reduced unwanted pregnancy their use was primarily for protection against sexually transmitted diseases. Vaginal poultices for contraception have been used by numerous cultures such as South American native women who inserted quinine-soaked bark strips into their vaginas (Pearson 1986).

In Innsbruck 1919, Ludwig Haberlandt conducted the first research that suggested exogenous hormonal control could be used as a contraceptive method thus paving the way for the development of oral contraceptives. Haberlandt produced infertile female rabbits by taking ovaries from pregnant rabbits and inserting them under the skin of the aforementioned female rabbits. He subsequently extracted copora lutea from pregnant cows and injected them into rabbits also resulting in infertile rabbits.

Margaret Higgins Sanger (1879-1966), an American birth control activist, sex educator, and nurse. (Source: Flickr Commons project, 2013).

Unfortunately, the motivation to promote the scientific investigation of contraception in the United States was born from eugenics policies. Eugenics is a pseudoscience developed by Francis Galton in the early 1900s with a racial bias for wealthy, white-protestant individuals to reproduce over other lower-income, racial, and ethnic groups. Eugenics was a popular doctrine adopted by the American scientific community to oppress and negatively impact marginalized families. The strongest proponent of contraceptive research was Margaret Sangar (pictured on the right) who used the establishments' embrace of eugenics to fuel support for the discovery of more effective and affordable contraception for women. In 1916 Sanger founded the first women's birth control clinic that focused on women in poverty, empowering them to make their own reproductive choices. She understood that birth control was THE fundamental women's rights issue writing that "forced motherhood is the most complete denial of a woman's right to life and liberty". Gloria Steinham (1998) was asked to comment on Sanger's eugenics connection and found it to be a strategy, saying Sanger

> adopted the mainstream eugenics language of the day, partly as a tactic, since many eugenicists opposed birth control on the grounds that the educated would use it more. Though her own work was directed toward voluntary birth control and public health programs, her use of eugenics language probably helped justify sterilization abuse. Her misjudgments should cause us to wonder what parallel errors we are making now and to question any tactics that fail to embody the ends we hope to achieve.

Women gained the potential for reproductive freedom thanks to Margaret Sanger's efforts. In 1958, Pincus et al. reported the successful use of oral contraceptives as a means of birth control, and in 1960 the first oral hormonal contraceptive pill, Enovid, was approved by the US Food and Drug Administration (FDA), [see below for more information on clinical trials that led to the FDA's approval]. Currently, approximately one-third of women worldwide use hormonal-action contraceptives (Anderson and Johnston 2023). Yet still, nearly half of the 210 million pregnancies that occur globally each year, are unintended (UN 2022). In the United States alone, a recent survey conducted by the CDC found the risk of unintended pregnancy of women aged 18-49 years is over 76% and over "60% of women had an ongoing or potential need for contraceptive services" (CDC 2021).

A biased oral contraceptive clinical trial was conducted in the US Territory of Puerto Rico.

First off, what is a clinical trial?

A clinical trial is defined as a study that compares the effect and value of intervention(s) against a control in human beings (Friedman, Furberg, and DeMets 2010). It is the best way to determine if a particular drug/treatment will work because the inclusion of a control group enables a direct comparison between using and not using the intervention. Ethical considerations arise during the design, implementation, and reporting of clinical trials. When considering a clinical trial, the following ethical criteria are essential: “value, scientific validity, fair selection of participants, favorable benefit/risk balance, independent review, informed consent, and respect for participants” (Friedman et al. 2010). Unfortunately the first clinical trials for oral contraceptives missed the mark on a few of these criterion.

The Puerto Rico Clinical Trial

Marks (Marks 2010) describes why women on the island of Puerto Rico were chosen for the large-scale oral contraceptive trial. There were big obstacles to setting up a clinical trial in Massachusetts (where initial small-scale research by Rock and Pincus had been conducted) which included legal restrictions on contraceptive research and an inability to find a large enough population of women willing to participate for the length of time needed. Puerto Rico seemed to be the perfect solution because several birth-control clinics were already established due to the combination of a high poverty rate exacerbated by the high birth rate and there were many willing participants. The study began in April 1956 with a total of 225 women, 125 of whom would serve in the control group using either conventional devices or no birth control. Over half of the participants left the trial for numerous reasons and were replaced with new volunteers and the study sites were expanded to Haiti and Mexico City.

The trial was biased from the start

The main benefactor of the birth control pill research was the staunch women's rights advocate Katherine Dexter McCormick. She recognized the importance of conducting trials for the pill. However, according to Marks (2003) from the start her bias of equating participants as lab models rather than human beings, is evidenced in her comment to Dr. Pincus regarding the clinical trial bottleneck problem being "how to get a cage of ovulating females to experiment with", written in a letter to Sanger in 1955. This attitude may have been shared by the lead researchers Pincus and Rock who did not provide full information to participants, withholding the fact that they were participating in a clinical trial in the first place, and were dismissive of their complaints of side effects saying they were "psychosomatic" because of the leading questions posed to participants. Their answer to the problem of large numbers of women dropping out of the trial was to ignore the issues and publish the results in terms of the number of menstrual cycles rather than individual women, thereby increasing the scale and making their results look more remarkable (Eig 2014).

Why don't all sexually active women use protection?

Concerns about side effects as well as negative attitudes about pleasure, desire, and sex stop many from seeking information. On a wider scale, these attitudes keep sex information from being distributed freely in schools and community organizations. Even though, many studies show giving birth control information to teenagers does not make them more likely to have sex (Mark and Wu 2022).

Unintended pregnancies occur disproportionately in young and poor women and are associated with increased incidences of maternal and child mortality and cycles of intergenerational poverty (Bearak et al. 2022). Moreover, birth control is not just a women's issue but societal messages neglect the impact that unprotected sex can have on men. It is also beneficial for men to be able to decide when and if they will father a child, as well as protect themselves from sexually transmitted infections.

Different methods of contraception

There are many types of contraception but none are perfect. The choice of which method to use comes down to multiple factors such as cost, ease of use, whether or not a physician is required for prescription/insertion, whether or not protection from sexually transmitted infections is sought as well, and potential side effects.

Methods can be divided into distinct categories based on their mode of action: fertility awareness methods, withdrawal, barrier methods, hormonal methods, IUDs, emergency contraception, and permanent methods. No method is 100% effective at preventing pregnancy but when used properly some are as high as 99% effective. Perfect efficacy of a method is only achieved when the method is correctly used each time and this rate is determined from clinical trials. Because people are not "perfect" each method is given a more realistic typical-use efficacy measure. This refers to the effectiveness of the method taking into account human error and is based upon real-world use. The following information about each type is from the Planned Parenthood website on birth control.

Withdrawal (Pulling Out)

Withdrawal refers to pulling the penis out of the vagina before ejaculation. If semen gets in the vagina, you can get pregnant. So ejaculating away from a vulva or vagina prevents pregnancy. But you have to be sure to pull out before any semen comes out, every single time you have vaginal sex, for it to work. This is challenging notes Arteaga and Gomez (2016), because it "requires men have somewhat precise control over and anticipation of ejaculation, as well as the wherewithal to remove the penis prior to sexual climax." If done properly this method has a 78% Typical Use Efficacy. A study conducted by Jones et al., (2014) found that only a minority of withdrawal users (12% of the entire sample) relied on the method exclusively, and most had also used an additional highly effective method; this contraceptive method was most common among the youngest women surveyed.

Fertility awareness methods

Fertility awareness methods (FAMs) are ways to track your menstrual cycle and fertile days to prevent pregnancy. Charting the basal body temperature and keeping track of a regular cycle (see chart below) allows one to determine the likelihood of being fertile. FAMs are also called “natural family planning” and “the rhythm method.” The days near ovulation are your fertile days — when you are most likely to get pregnant. So people use FAMs to prevent pregnancy by avoiding sex or using another birth control method (like condoms) on those fertile days. FAMs have a typical-use efficacy ranging from 77% to 98%. A review by (Duane et al. 2010) reported that with correct use the FAM method had a typical-use efficacy of 85%, noting that recognizing the beginning of the fertile window is more difficult than the end due to the variability of the follicular phase. The better you are about using FAMs the right way — tracking your fertility signs daily and avoiding sex or using birth control on fertile days — the more effective they'll be. But like all methods besides abstinence, there's a chance that you'll still get pregnant, even if you always use them perfectly.

Barrier methods

Barrier methods rely on the ability to physically block sperm from reaching the ovulated egg, thereby preventing fertilization. These include condoms, diaphragms, cervical caps, and spermicides.

Condoms – 87% Typical-Use Efficacy. Small, thin pouches that cover the penis during sex and collect semen. Condoms must be put on correctly before sex. The added benefit is that some* condoms can offer protection against some sexually transmitted infections. "Pathogenic microorganisms including HIV cannot pass through high-quality male latex condoms" (Batar and Sivin, 2010) (* Lambskin condoms do NOT protect against STDs, because there are tiny holes in the lambskin that are small enough to block sperm but big enough to let bacteria and viruses through. So it's best to use latex condoms to help prevent both STDs and pregnancy.)

Diaphragm – 83% Typical-Use Efficacy for women who have not yet given birth, 78% effective for women who have given birth. It is a shallow cup shaped like a little saucer that's made of soft silicone. You bend it in half and insert it inside your vagina to cover your cervix. For a diaphragm to work best, it must be used with spermicide (a cream or gel that kills sperm). Less than 1% of women use diaphragms and most pharmacies no longer carry diaphragms (Schwartz 2019).

Cervical Cap – 86% Typical-Use Efficacy for women who have not yet given birth. For people who have given birth, the cervical cap is 71% effective. A cervical cap is a little cup made from soft silicone and shaped like a sailor's hat. It must be fitted by a clinician. You put it deep inside your vagina to cover your cervix. It is an alternative to the sponge for those with "some vaginal abnormality" and "can be inserted up to one day before coitus…and left in place for more than 24 hours allowing for repeated intercourse" (Batar and Sivin 2010). For a cervical cap to work best, it must be used with spermicide. The FemCap, currently available, requires a prescription in the United States (Schwartz 2019).

The Sponge – 86% Typical-Use Efficacy. The birth control sponge (aka the contraceptive sponge or "the sponge" for short), is a small, round sponge made from soft, squishy plastic. You put it deep inside your vagina before sex. The sponge covers your cervix and contains spermicide to help prevent pregnancy. Each sponge has a fabric loop attached to it to make it easier to take out. It may remain in place for up to 30 hours but "removal should not be attempted until the passage of six hours following coitus" (Batar and Sivin, 2010). The Today sponge is available in the United States and contains N-9 1 spermicide that is released over the 24-hour period the sponge is left inserted in the vagina (Schwartz 2019).

Hormonal methods

Oral contraceptives work to **block ovulation by acting on the HGP pathway**. For a short review on this see the website.

Hormonal contraceptives involve the administration of synthetic versions of progesterone (**progestin**) with or without estrogen to inhibit ovulation and thicken cervical mucus to block fertilization. Progestin blocks GnRH from the hypothalamus (see image on right depicting HPG pathway), thus preventing ovulation. It also reduces cervical mucus permeability and endometrial receptivity.

Progestins are derived from 19 nor-testosterone and include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, norethynodrel, desogestrel, norgestimate, and gestodene (Horvath, Schreiber, and Sonalkar 2018). Estrogen also inhibits GnRh release and blocks FSH preventing the formation of the dominant follicle. Estrogen also reduces irregular bleeding and therefore it is often used in combination with progestin to produce a more consistent and regular period. Three different types of estrogens are used: ethinyl estradiol (EE), mestranol, and estradiol valerate (Horvath et al., 2018). Keep in mind that there are complications attributable to both progestin and estrogen (see the contraindications section below).

Implant (Nexplanon) – 99% Efficacy

The birth control implant is a tiny, thin rod about the size of a matchstick. The implant releases synthetic progestin into your body. A nurse or doctor inserts the implant into your arm and that's it — you're protected from pregnancy for up to 5 years. There have been reports of issues with the implant however, "events associated with the insertion, localization, and removal of the Nexplanon were rare" (Reed et al. 2019).

It is a "get-it-and-forget-it" birth control making it super convenient. If you decide you want to get pregnant or you just don't want to have your implant anymore, your doctor can take it out. You're able to get pregnant quickly after the implant is removed. For more information on Nexplanon see Palomba et al. (2012).

Hormone Shot – 96% Efficacy

The Depo shot (AKA Depo-Provera) is an injection of progestin that you get once every 3 months. Most of the time, a doctor or a nurse must give you the shot. So you have to make an appointment at a health center, and then remember to go to the appointment. But you also may be able to get a supply of shots at the health center to bring home and give yourself. For more information on Depo-Provera see Westhoff (2003).

Hormone Ring – 93% Typical-Use Efficacy

A small, flexible ring inside your vagina, and prevents pregnancy 24/7 by releasing hormones into your body. There are two types, NuvaRing and Annovera which both disperse synthetic estrogen and progestin equally. The NuvaRing lasts for up to 5 weeks and you take your old NuvaRing out of your vagina and put in a new one about once a month, depending on the ring schedule you choose. One Annovera ring lasts for 1 year (13 cycles). You put the Annovera ring in your vagina for 21 days (3 weeks), then take it out for 7 days. For more information on the NuvaRing see (Roumen 2008).

Hormone Patch – 93% Typical-Use Efficacy

The transdermal patch is worn on certain parts of your body, and it releases a combination of progestin and estrogen through your skin that prevents pregnancy. To get the patch's full birth control powers, you have to use it correctly. Making a mistake — like forgetting to refill your prescription or not putting on a new patch on time — is the main reason why people might get pregnant when they're using the patch.

Hormone Pill – 93% Typical-Use Efficacy but it is important to note that certain drugs can interfere with the effectiveness of the pill because it is metabolized via the hepatic cytochrome P450 pathway (Teal and Edelman 2021). For example, antibiotic rifampin; certain antifungals that are taken orally for yeast infections; certain anti-HIV protease inhibitors; certain anti-seizure medications; & St. John's Wort can decrease the effectiveness. There are some health risks associated with the pill. Women over 35 who smoke should not use the pill due to an increased risk of abnormal blood clot formation. There is also an elevated risk (20-30%) of developing breast cancer when using progesterone-only pills (Fitzpatrick et al. 2023). Birth control pills come in a pack, and you take 1 pill every day. The pill is safe, affordable, and effective if you always take your pill on time. "Originally, birth control pills were dosed with 21 days of active drug and a 7-day placebo week to trigger a monthly withdrawal bleed, meant to mimic the natural menstrual cycle" (Teal and Edelman, 2021). Problems associated with the placebo week led to the development of pills with shorter placebo periods (4 days) or none at all (continuous-dose pills).

Good news! You no longer need a prescription for birth control pills. The **Opill** is an over-the-counter pill now available. The FDA recently approved the first over-the-counter birth control pill norgestrel (Opill). Opill, also known as the "mini-pill," contains a single hormone, progestin, and is taken daily. Research conducted by Anna Glasier et al. (2022; 2023) was used as part of the FDA approval process and highlights the mechanism of action of norgestrel and how missing a single dose of norgestrel does not hurt efficacy.

Q&A with Dr. Anna Glasier, OBE, Ph.D., the first Women's Health Champion for Scotland.

College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK

Professor Anna Glasier, Ph.D.

What drew you to studying women's reproductive health specifically contraception? Scotland has a long tradition of interest in Women's Reproductive Health. When I started training in obstetrics and gynecology the MRC Unit of Reproductive Biology in Edinburgh had just moved into a new building physically attached to the maternity and gynecology hospital services, so it was hard to avoid developing a strong interest, including a research interest in RH. Moreover, there were individual clinicians and scientists (like David Baird and Roger Short) who were inspirational.

What have you enjoyed most about your career and what is it like to be recognized (receiving the OBE) for your work? I have been extremely lucky to have had such a great career. I enjoyed almost every aspect of my work including seeing patients. However, my career as a clinical researcher led to my being involved with a lot of international work which was very stimulating. I worked for many years with the World Health Organization in Geneva and with the Population Council in New York. For me, being recognized for my expertise by scientific organizations is important and fulfilling. Getting a paper published in a high-impact journal such as the Lancet or New England Journal of Medicine is always a great reward for research efforts. I am proud of the role I played in the UK and the US in getting emergency contraception and more recently progestogen-only pills available without needing to see a doctor. Finally, I was delighted to be asked to become the Women's Health Champion for Scotland at a very late time in my career.

How do you see the career path for women in science has changed since you began and what do you hope for the future? I think it has become easier than it used to be for women to have a career in science. Part-time working or job-sharing has become much more acceptable allowing women to have a career and a family. Many organisations have a policy of encouraging women to participate at a senior level.

What advice do you have for future women scientists? I am most familiar with doing clinical research. My advice to junior clinicians is to accept every opportunity to participate in clinical research, recruit patients for colleagues who are doing studies, and take an active interest in their research and you might end up having a career as enjoyable as mine.

Contraindications of hormonal contraceptives

A contraindication is a specific factor that makes the birth control method potentially harmful for a particular individual and therefore they should not use the particular method. For a long time, physicians have been aware of contraindications associated with hormonal combination methods (estrogen + progesterone), as well as estrogen-only methods. There are minimal medical conditions that contraindicate progestogen-only contraceptives. Specifically, instances of problems associated with blood flow have been noted such as an increased risk of venous thromboembolism as well as increased cardiovascular disease, particularly for women who smoke and/or are obese (Serfaty 2019). A recent study by Roland et al., 2024 found that women who used the birth control shot Depo-Provera (medroxyprogesterone acetate) for an extended period are more than five times more likely to develop brain tumors.

List of contraindications for hormonal contraceptives (keep in mind this is not an exhaustive list)

- Blood clots, e.g. deep vein thrombosis, pulmonary embolism, or clotting disorders
- Stroke or heart attack
- Certain cancers, e.g. breast cancer or liver cancer
- Liver disease
- Migraines with aura (neurological symptoms)
- High blood pressure that is not well managed
- Diabetes with complications
- Abnormal uterine bleeding
- An increase in the risk of intracranial meningioma has been found in Depo-Provera users

It is important to note that for women with underlying health conditions who want to use a hormonal method (e.g. a woman with a history of breast cancer choosing combined hormonal contraceptives) their physicians/nurse practitioners will be able to advise them.

Are hormonal contraceptive methods available for men? The only currently available contraceptive option for men is condoms. Research is underway that includes a testosterone plus progestin topical gel which suppresses sperm count (Teal and Edelman, 2021).

Intrauterine devices

An intrauterine device (IUD) inserted into the uterus blocks fertilization and implantation. There are two types of IUDs, copper and hormonal (progestin-only). The copper IUD directly interferes with sperm and the hormonal IUD also interferes with sperm and ovulation. It's long-term and reversible. An IUD has to be put in by a doctor, nurse, or other health care provider and the cost may be covered by insurance. Your IUD will protect you from pregnancy for 3 to 12 years, but your doctor or nurse can take it out any time before that if you like.

Permanent methods (Sterilization)

Permanently preventing pregnancy involves surgery performed by a physician or clinician. The cost of sterilization varies and depends on where you get it, what kind you get, and whether or not you have health insurance that will cover some or all of the cost. Over one-third of women choose sterilization as their contraceptive method, making it the most common method

(Mosher and Jones 2010). There are two types of female sterilization: tubal ligation and bilateral salpingectomy.

1. Tubal Ligation – Surgical procedure that permanently closes, cuts, or removes pieces of your fallopian tubes.
2. Bilateral salpingectomy – Surgical procedure that removes your fallopian tubes entirely.

Emergency contraception

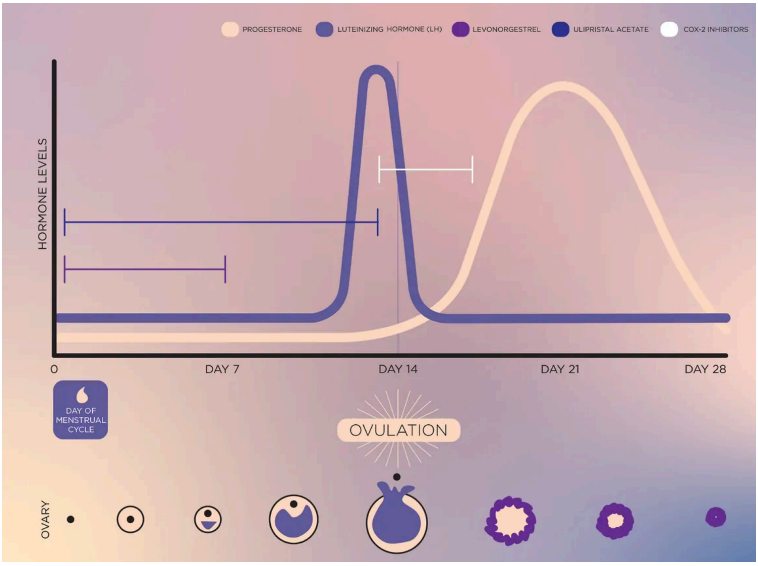
Unfortunately, there are a lot of misconceptions surrounding emergency contraception (EC). EC does not affect implantation or harm the embryo instead it prevents fertilization by blocking ovulation (Gemzell-Danielsson, Rabe, and Cheng 2013). As defined by the World Health Organization, EC methods are "methods of contraception that can be used to prevent pregnancy after sexual intercourse. These are recommended for use within 5 days but are more effective the sooner they are used after the act of intercourse." The mode of action is to prevent or delay ovulation and modulate sperm activity without affecting an established pregnancy.

Plan B is a high dose of levonorgestrel (progestin) that has an 89% efficacy rate and is available over the counter for up to 72 hours after unprotected intercourse. It has a limited window of action. Studies show that levonorgestrel has a significant inhibitory effect on ovulation taken two days before the LH surge without affecting endometrial receptivity

(Endler, Li, and Gemzell Danielsson 2022). Plan B is not recommended for women with a BMI greater than 30 (Cleland et al. 2020)

The drug ulipristal acetate (UPA) sold under the brand name Ella has a very high efficacy (99%) even when the probability of conception is at its highest because it behaves as an agonist when progesterone levels are low, but as progesterone increases, UPA acts antagonistically, inhibiting the LH surge, therefore, preventing ovulation (Rosato, Farris, and Bastianelli 2016). It is also indicated for use up to 120 hours after unprotected intercourse. Yet you must have a prescription to obtain UPA and it is not recommended for women with a BMI greater than 35.

The copper-bearing IUD sold under the name ParaGard can also act as an EC by causing a chemical change that prevents fertilization. It appears to be highly effective as long as it is inserted within the five-day window, studies have shown that over 99% of those who use a copper IUD as an emergency contraceptive method do not become pregnant (Goldstuck and Cheung 2019).



Available emergency contraceptive drugs act over different periods of the fertile window. Some, like levonorgestrel, act before the luteinizing surge begins, while ulipristal acetate acts from before the LH surge until the peak of the surge. COX-2 inhibitors block ovulation after the LH surge, which is most critical since ovulation occurs right at this point.

We must keep in mind that not all women can freely make decisions regarding their reproductive health. As noted in the 2022 UN Population Fund Annual Report nearly 25% of all women, where data are available, are unable to say no to sex. A recent study found a significant relationship between unmet contraception needs and when women's healthcare choices were decided on by their male partners (Agyekum et al. 2022). There is also limited access to contraception in some regions of the world and even in the United States of America pharmacists have illegally refused to fulfill birth control prescriptions and are often encouraged to do so by religious doctrine as exemplified in the essay entitled "Pharmacist refusal to provide contraceptive services" by Baalmann (Baalmann 2022).

Think, Pair, Share

What are some of the reasons that prevent women from using contraception?

How is contraceptive access connected to gender equity and empowerment?

Under what circumstances might a woman choose one contraceptive method over another?

Compare the health risks of going through an unintended pregnancy to the health risks of using hormonal contraceptives.

Deeper Questions

Why might a woman falsely think that if they are using birth control they cannot say no to sex?

Why do you think that there are numerous contraceptive options for women but not for men and what might explain the fact that twice as many women seek sterilization as compared to men?

What forces exist today that resist efforts to make safe, reliable contraception available?

Key terms

Barrier method
  Condom
  Contraindication
  Depo-Provera
  Diaphragm
  Emergency contraception
  Fertility awareness method
  Intrauterine device
  Levonorgestrel
  Nexplanon
  NuvaRing
  Typical-Use efficacy
  Perfect Use efficacy

Spermicide
Sterilization
Transdermal patch
Ulipristal acetate

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Suggested Reading

"Taking Charge of Your Fertility" by Toni Weschler – This comprehensive guide provides in-depth information about fertility awareness-based methods of contraception and natural family planning. It includes charts, illustrations, and practical advice for tracking your menstrual cycle.

"The Pill: Are You Sure It's for You?" by Jane Bennett and Alexandra Pope – This book explores the history and potential side effects of oral contraceptives (birth control pills) and provides information to help individuals make informed decisions about their use.

"Devices and Desires: A History of Contraceptives in

America" by Andrea Tone – This book delves into what it was like to buy, produce, and use contraceptives during a century of profound social and technological change.

"The Reproductive Health of Adolescents" by Jennifer L. Gibson and Judith S. Seifert – Geared toward healthcare professionals, educators, and parents, this book covers a wide range of topics related to adolescent reproductive health, including contraception, sexual education, and healthcare access.

Interesting Podcast

The Daily: How the birth control pill got over the counter

8.

PREGNANCY

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Describe the process of fertilization
- Compare the contribution of egg and sperm in the zygote
- Describe implantation
- Discuss the role of the placenta during pregnancy
- Describe how pregnancy test kits work
- Explain how the due date for pregnancy is determined
- List the changes in a woman's body that occur during pregnancy
- Recall the complications that may arise during pregnancy
- Recognize the importance and limitations of prenatal care
- Describe the role midwives can play
- State how pain can be dealt with during labor
- Explain breastmilk and the importance of breastfeeding

- Discuss hypotheses about the evolution of mammary glands

Pregnancy is a significant and complex life event that has profound physical, emotional, and social implications

Thanks, mom! We can all attribute our existence to our mother and to the amazing phenomenon called pregnancy. It is a period of major physical and emotional change for women and thus pregnancy is a big deal! Pregnant women are in great need of social support and although it is a normal physiological process complications from pregnancy are the leading cause of death globally among adolescent girls aged 15-19 years. Furthermore, the United States has the highest maternal mortality rates among developed countries, particularly for women of color (OECD 2023). Being informed and having the ability to process the information, ask questions, and have the ability to discuss information with a healthcare professional before a decision regarding pregnancy is made is ideal (Moore 2016). In this chapter, the stages of pregnancy from fertilization to birth are discussed.

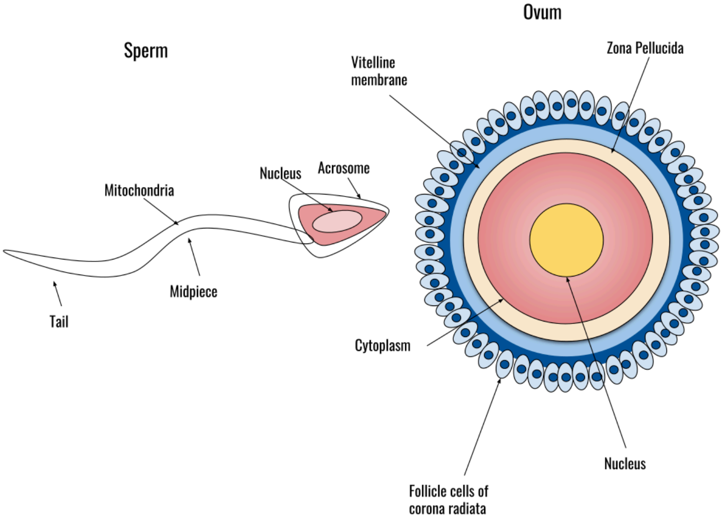
From conception to 12 weeks

Fertilization

Fertilization, first described in detail from studying sea urchins (Hertwig 1876), occurs when the egg and sperm fuse. However, compared to sea urchins, mammals experience internal fertilization making understanding the process challenging. Researchers are still working to unlock some of the mysteries surrounding the process. In humans, coitus (the penetration of the vagina by the penis) may result in the ejaculation of sperm, of which approximately 200 from the initial 280 x 106 sperm ejaculated into the vagina reaches the ampullary region of the oviduct (Boitrelle et al. 2021). Intrauterine insemination (IUI) may also be used whereby a minimum of 6.7 million sperm are inserted into the uterus for successful fertilization, using a small catheter (Higdon et al. 2008).

Recall that the follicle ruptures during ovulation and the mature ovum (egg) is released from the ovary into the peritoneal cavity where the fimbriae, finger-like projections at the end of the fallopian tube (oviduct) pick up the released egg. There it awaits the arrival of sperm which swim toward the oviducts. Sperm are assisted by the muscular activity of the uterus and the ciliary beating of the oviduct. As sperm travel toward the oviduct they must experience capacitation (incubation) to undergo the acrosomal reaction. The

acrosomal reaction is an ectocytotic event (contents of a cell vacuole are released to the exterior through fusion of the vacuole membrane with the cell membrane) that makes it possible for the sperm to fuse with the egg. The **acrosome** is located in the anterior portion of the sperm head and contains enzymes that assist in the penetration of the extracellular matrix (**zona pellucida**) of the egg (see figure below).


Ovum
Sperm
Vitelline membrane
Zona Pellucida
Nucleus
Acrosome
Mitochondria
Midpiece
Tail
Cytoplasm
Nucleus
Follicle cells of corona radiata

Anatomy of the human egg and sperm.

Data suggest that both the ovary and egg secrete chemotactic substances to help attract the sperm to the egg (Sun et al. 2005). Once the sperm reaches the egg the zona pellucida binds the sperm with the assistance of **ZP3**, a glycoprotein on the zona pellucida that binds to sperm along with additional proteins. The binding of ZP3 along with progesterone induces the acrosomal reaction. Once the acrosomal reaction happens fusion of the sperm cell membrane with the egg cell membrane occurs.

Polyspermy, the fusing of more than one sperm to an egg, can result in the lethal problem of triploidy (having an extra set of chromosomes). Polyspermy is blocked in mammals by three mechanisms according to Evans (2020):

Block 1) Sperm travel through the uterotubal junction where they are exposed to oviducal epithelial cells/secretions that inhibit many sperm;

Block 2) Exocytosis of cortical granules from the cortex of the egg inhibits zona pellucida from supporting further sperm binding; and

Block 3) Membrane block induced by increased Ca2+ in the cytosol of the egg (mechanism not yet understood).

Egg activation

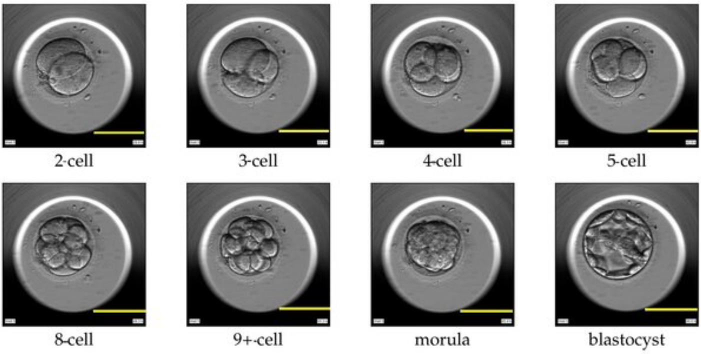
Egg activation occurs after fertilization has taken place, following the fusion of the sperm and egg membranes. An **increase in Ca2+** concentration (the calcium wave) in the cytoplasm triggers the resumption of meiosis in the mature oocyte and activates the development of the embryo. The male pronucleus enlarges while the oocyte nucleus completes its second meiotic division. Each pronucleus replicates its DNA and they migrate toward one another. They meet and the chromatin condenses into chromosomes that orient themselves on a common mitotic spindle. The sperm contributes a pair of centrioles that are duplicated, one of each moves to each pole of the egg cell, replacing the those of the egg cell. A series of metabolic events are also triggered thanks to the calcium wave.

Rearrangement of the egg cytoplasm

The haploid male pronucleus is necessary for egg activation and contribution to the diploid genome but the rest of the sperm plays no major role in embryogenesis. The egg contains key morphogenic determinants that become segregated into specific cells during cleavage. These lead to the activation and/or repression of specific genes and are known as maternal factors, also known as maternal effect genes. How maternal effect genes work was first described by Nüsslein-Volhard et al. (1980) in Drosophila however it took another 20 years before similar genes were described in mammals (Christians et al. 2000). Christine Nüsslein-Volhard earned the Nobel Prize in Physiology or Medicine in 1995 for her research on the genetics of embryonic development in *Drosophila*. See her Nobel Laureate website.

The embryo and cleavage

All animal species undergo **cleavage**, a series of mitotic divisions whereby the egg cytoplasm is divided into numerous smaller nucleated cells (image of cleavage below). In mammals, the first cleavage begins about a day after fertilization and happens as the cilia in the oviduct push the embryo toward the uterus. A key distinction between mammals and all other animals is that they go through a 16-cell **morula** stage consists of a small group of internal cells surrounded by a larger group of external cells. In non-mammalian animals, embryonic development varies significantly, and they may not go through a morula stage like mammals. For example, birds do not form a morula instead they form a **blastoderm** which is a disc-shaped structure that forms on top of the yolk. From the morula, most of the external cells become the **trophoplast** whose cells will form the embryonic portion of the placenta, the chorion. The **inner cell mass** gives rise to the embryo and its associated yolk sac, allantois, and amnion. At the 32-cell stage, the structure is called the **blastocyst** (see figure below) and by the 64-cell stage, the inner cell mass and trophoblast become separate cell layers. The cells in the inner cell mass are pluripotent and are called embryonic stem cells; they will ultimately give rise to each of the 200 cell types in our bodies. The trophoblast cells will be involved in the uterine invasion (described below) and the formation of the extraembryonic membranes that are a feature of all amniotes.



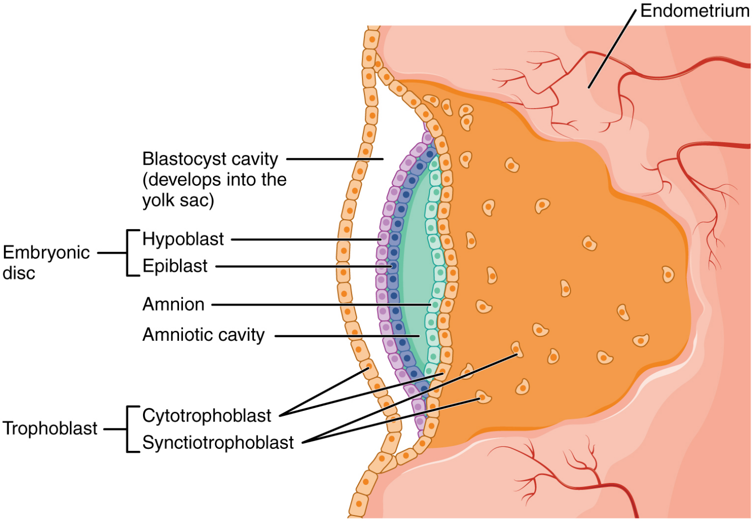
Cell cleavage stages of human embryo development. Scale bar: 100 μm.

Gastrulation in mammals

Approximately 14 days post fertilization the embryo begins gastrulation whereby the blastocyst is transformed into a **gastrula**. Tam and Behringer describe gastrulation in the mouse (Tam and Behringer 1997): during gastrulation the body plan is formed to serve as a "blueprint for the subsequent morphogenesis of the embryo", making the anterior-posterior axis obvious and creating the three germ layers: ectoderm, mesoderm, and endoderm through cell proliferation and differentiation. The germ layers are then "partitioned into domains of progenitor cells that give rise to the major tissue types". As for humans, recent research by Tyser et al. (2021) found that "the signaling pathways of gastrulating cells transitioning from epiblast to mesoderm was broadly conserved between humans and the mouse...” with differences in regulation.

Implantation of the blastocyst

Humans are eutherian mammals, a group characterized by the development of the placenta that allows for advanced development as compared to non-eutherian mammalian monotremes (egg laying, e.g. the echidna) or marsupials (complete development in a pouch, e.g. opossum). In eutherians, implantation occurs when the embryo attaches itself to the endometrial surface of the uterus and invades the epithelium and the placenta will form. This is referred to as a “**proinflammatory process**” and is reviewed by Kim and Kim (2017). It is a time-sensitive event with a specific “**window of implantation**” where the blastocyst and receptive uterus communicate through a “synchronized molecular dialogue”. For humans, this window lasts from days 16-22 of a 28-day cycle when the endometrium has been primed to accept the blastocyst. This is a critical time during pregnancy and most pregnancy losses (miscarriages) occur soon after implantation.


Endometrium
Blastocyst cavity (develops into the yolk sac)
Embryonic disc
Hypoblast
Epiblast
Amnion
Amniotic cavity
Trophoblast
Cytotrophoblast
Synctiotrophoblast

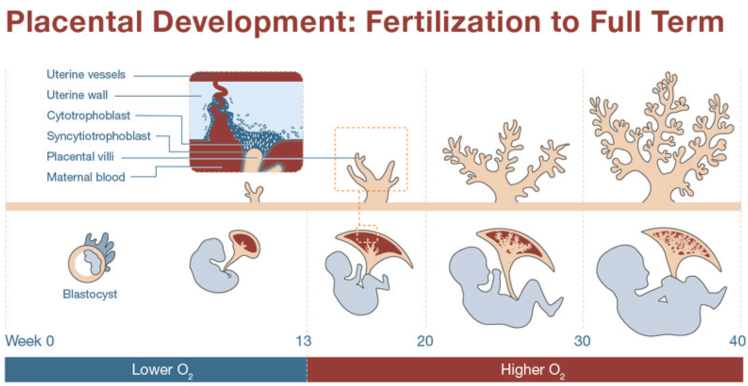
Implantation, stage in the embryonic development of mammals in which the blastocyst attaches, adheres and invades the endometrium, image from OpenStax College on WikiCommons.

Approximately 1-3 days after the morula enters the uterine cavity implantation is initiated with the loss of the zona pellucida. The morula becomes a blastocyst that adopts a more irregular surface with microvilli. The blastocyst touches the implantation site adhering itself at the uterine epithelium creating a pro-inflammatory reaction mediated by prostaglandins. It is during this process that the blastocyst differentiates into an inner cell mass (**embryoblast**) and trophoblast (pictured above). Cytokines (regulatory peptides) and growth hormones interact between the trophoblast and uterus during attachment and both cell adhesion molecules and integrins (transmembrane glycoproteins) play a key role in successful adhesion of the trophoblast to the endometrial epithelium.

According to Kim and Kim (2017) once attached to the epithelium the trophoblast cells become **cytotrophoblast** cells and **syncytiotrophoblast** cells. The cytotrophoblast cells produce enzymes so the syncytiotrophoblast cells can invade and migrate into the thickened and vascularized endometrial lining, penetrating the basement membrane (pictured above). The syncytiotrophoblast cells destroy and reconstruct the maternal spiral arteries to increase the blood supply and oxygen for the fetus. The syncytiotrophoblast cells create the placental villi with the aid of growth factors, cytokines, and enzymes while modulating the maternal immune response. These villi will begin to establish fetal-maternal communication, orchestrating the complex biomolecular interactions that result in the formation of the placenta.

The placenta

The placenta is comprised of the **chorion, amnion, and umbilical cord** and serves as an interface between the mother and developing fetus, facilitating the exchange of oxygen, nutrients, and waste products and assisting in maternal physiological adaptations to pregnancy. The umbilical cord is a critical link between the developing fetus and the maternal circulation during pregnancy, and it ensures the exchange of substances necessary for fetal growth and well-being. It contains two arteries and one vein. The two umbilical arteries carry deoxygenated blood and waste products away from the fetus to the placenta, while the umbilical vein carries oxygenated blood and nutrients from the placenta to the fetus. The fluid-filled amnion (amniotic sac) surrounds the embryo providing a protective cushion. The placenta develops as the pregnancy progresses (see image below).


Placental Development: Fertilization to Full Term
Uterine vessels
Uterine wall
Cytotrophoblast
Syncytiotrophoblast
Placental villi
Maternal blood
Blastocyst
Week 0
13
20
30
40
Lower O_2
Higher O_2

The placenta develops as the pregnancy progresses. Image from the Human Placenta Project, permission granted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

In a review of the evolution of the placenta, the organ is described as "the least conserved and the most rapidly evolving mammalian organ" (Roberts, Green, and Schulz 2016). Several genes involved in placental development are imprinted which means that they are expressed based on parent of origin through epigenetic control mechanisms (Hanna 2020). The outer layer of the trophoblast forms the chorion which produces human chorionic gonadotropin (hCG) that plays a crucial role in producing progesterone maintaining early pregnancy until the placenta can take over hormone production. Issues that may arise impact the development of the placenta can lead to severe problems for the embryo and often underlie miscarriages (Rossant and Cross 2001). A serious effort to better understand the placenta (the Human Placenta Project) was launched in 2015 by the NIH setting aside over $40M in funding (Reardon 2015).

As discussed above, the placenta is a critical link between the fetus and mother and when it does not develop properly there can be inadequate blood supply (ischemia). Dr. Laura Clamon Schulz and associates examined the effect of undernutrition during early gestation on placental development in mice and found food restriction from three weeks before mating through 11.5 days post-conception alters placental structure (Van Gronigen Case et al. 2021).

Q&A with Dr. Laura Clamon Schulz, Ph.D.

Associate Professor of Obstetrics, Gynecology and Women's Health,

Director ObGyn Research Success Core, Director SOM OneHealth Biorepository at the University of Missouri

Dr. Laura Clamon Schulz, Ph.D.

What drew you to studying women's reproductive health and specifically the placenta? In college, I fell in love with a class in comparative physiology. I thought (and still think) that studying the diversity of animal physiology, and the variety of solutions animals have developed to survive in their particular environments, is a powerful tool for understanding how our own bodies function. And so I joined the laboratory of Dr. Janice Bahr in graduate school for the chance to work with pregnancy in American Black Bears, and that's where I became a reproductive physiologist. After a postdoc studying pregnancy in bats, I moved to Missouri, in part for family reasons, and got the opportunity to do a second postdoc with a National Academy of Sciences member, Mike Roberts. As it turns out, I stuck with studying pregnancy and questions about how the placenta forms, even though I use laboratory mice and cell culture systems, and try to address health-related questions. I switched largely because of where I found job and funding opportunities, but I have become passionate about being able to contribute to pregnancy health.

What have you enjoyed most about your career? I love the thrill of figuring out something new – whether it is just getting a new technique to work, or realizing how all the data fit together to reveal a new truth. But to be honest, those joys are fleeting, and the most sustained joy comes from mentoring and seeing my student's accomplishments and their growth is incredibly fulfilling.

How do you see the career path for women in science has changed since you began and what do you hope for the future? It is hard to compare, as I am not a student now, and I was not a mid-career scientist then. That is, I can't tell if the reductions in casual sexism that I've experienced are because of my age or because things have gotten better, but I hope it's the latter. At my University I see more women in leadership positions now. I recall there being only one woman professor in my undergraduate Biology department in the 90s, just my graduate advisor in her department, and just one female department chair in the School of Medicine when I arrived here in the late 2000s

What advice do you have for future women scientists? I would urge women not to be scared off because they want to have a family and a scientific career. I don't want to minimize anyone else's struggles, and it hasn't been without its challenges, but I think the perception of work-life balance issues has been more of a barrier than actual balance issues in my career. Granted, it's much easier if one has an equal partner. I also would urge future scientists to craft a professional demeanor that feels true to themselves. As a woman, you will always be told you are too something (quiet, loud, serious, silly) and it's better to spend your time trying to be a good scientist and colleague than to please all of them, which is impossible anyway.

Organogenesis

By the fourth week of pregnancy, **neurulation** occurs (the formation of a rudimentary central nervous system). This happens through a complex interplay of gene expression and environmental factors (e.g. dietary folic acid) starting with the formation of the neural plate, then the neural groove, and ultimately the neural tube which runs along the embryo's midline and will give rise to the brain and spinal cord. Some cells from neural folds separate and become neural crest cells that differentiate into the peripheral nervous system. By the sixth week, eyes begin to form and at the end of the eighth week, all organ systems have begun formation. For a view of the stages of human embryonic development see the Multi-Dimensional Human Embryo site.

Determination of pregnancy

One of the first indications that a woman may be pregnant is a missed period or the absence of menstruation. This is not the most reliable sign of pregnancy because there are many reasons for a late or skipped period other than pregnancy. If however there is a combination of factors such as elevated basal body temperature post ovulation, fatigue, nausea, and tender breasts then one may be pregnant. The easiest way to find out is to use a **home pregnancy test**. These over-the-counter tests indicate the **presence of hCG** in the urine which can be detected as early as 10 days post-conception. When used properly these tests are highly accurate, however they can produce false-negative or false-positive results. Timing is important and if in doubt confirming the result with a healthcare provider is essential.

Clinicians can look for additional early signs of pregnancy during a pelvic exam such as a softened cervix and color changes in the vagina (more blue than pink). Thick mucus discharge from the vagina may be an indication of the formation of a cervical plug (mucus that blocks the opening of the cervix). An ultrasound can confirm pregnancy as early as five weeks however most physicians will wait until 12 weeks to perform an ultrasound.

Timing of pregnancy

In mammals there is a relationship between the length of time it takes to go from fertilization to delivery (gestation period) and whether or not the neonate is altricial (relatively immature, i.e. usually hairless, and their eyes are often closed) or precocial (relatively developed, i.e.. eyes fully open and operating). For precocial species (e.g. elephants, moose, and primates) gestation periods are “on average approximately four times longer than in altricial species for any given maternal body size” (Martin and MacLarnon 1985). Generally, precocial species give birth to singletons whereas altricial species give birth to multiples in litters. It is hypothesized that the increased length of the gestation period in precocial mammals results in increased development of the central nervous system (Sacher and Staffeldt 1974). However, in humans, the gestation length is approximately nine months which is “shorter than expected based on how much growth the neonatal brain must achieve to reach adult size” perhaps due to the metabolic constraints between the developing fetus and the mother (Dunsworth et al. 2012).

How long a person is pregnant is the actual duration of pregnancy, starting from the date of conception (fertilization) to the time of delivery. This is related to the gestational age which is calculated from the first day of the woman’s last menstrual period (**LMP**). Although conception usually occurs about two weeks later the LMP approach is used because the exact date of conception is often challenging to determine but the LMP is usually more easily recalled and recorded. The developmental age is the number of weeks since fertilization and thus the gestational age is usually two weeks later than the developmental age. Terminology is often confused but it is important to understand the distinction between an embryo, fetus and infant. The term embryo is used from fertilization to 10 weeks gestational age, fetus from 10 weeks to birth and infant is used from delivery until one year of age.

Pregnancy is divided into three trimesters, each consisting of three calendar months.

- The first trimester: Weeks 1 to 12
- The second trimester: Weeks 13 to 27
- The third trimester: Weeks 28 to 40 (or until birth)

Infants delivered prior to 37 weeks of gestation are considered **preterm**, while those after 42 weeks are considered **post-term.**

The risk of multiple complications is much greater for premature infants and it is important to note that in regards to preterm birth incidences "there are significant racial and ethnic disparities. Black race is an established risk factor for spontaneous preterm birth, and preterm birth rates in the United States are 48% higher among non-Hispanic black women compared to women of other racial groups" (Purisch and Gyamfi-Bannerman 2017). In California, a recent study found that the risk of infant mortality was double for African Americans compared to whites (Ratnasiri et al. 2020). This is likely due to differences in access to prenatal care for people of color as well as "racism, and chronic stress" (Hill, Artiga, and Ranji 2022). Post-term pregnancy is also associated with increased problems including neonatal mortality and significant risks to the mother (Galal et al. 2012).

Changes during pregnancy

As stated in the book "Our Bodies, Ourselves" rather than a medical problem, "pregnancy is a natural process… a full-body experience… every organ system adapts" and thus pregnant women experience several physiological changes. There are several common issues associated with pregnancy including back pain, edema, hemorrhoids, pica, round ligament pain and varicose veins.

Physiological changes during pregnancy (Carlin and Alfirevic 2008)

Cardiovascular – cardiac output increases by 30-50% and systemic vascular resistance decreases during pregnancy. This may lead to edema (swollen ankles and fingers).

Pulmonary – There is an increase of 30 to 40% in tidal volume during pregnancy despite the fact that total lung capacity is decreased by 5% due to the elevation of the diaphragm.

Renal – Kidneys increase in size and the ureters dilate during pregnancy. The glomerular filtration rate (GFR) increases by 50% as a result of increased GFR blood urea nitrogen and creatinine decrease by about 25%. Urinary frequency increases as a result of pressure from the enlarging uterus on the bladder.

Hematology – The plasma volume increases by 50%, and the red blood cell volume increases by 20 to 30%, which leads to a decrease in the hematocrit the white blood cell count increases during pregnancy.

Skin – Numerous changes in skin color occur during pregnancy including spider angiomata and hyperpigmentation of nipples thanks to increased estrogen.

GI tract – Elevation in serum progesterone and estrogen levels is responsible for smooth muscle relaxation in the GI tract leading to nausea and vomiting, termed morning sickness even though it can occur anytime during the day. This usually resolves by 14 to 16 weeks gestation. Prolonged gastric emptying times can lead to reflux. Enlarged bowel leads to increased water absorption and constipation.

Musculoskeletal – Hormones cause the ligaments that hold the sacroiliac joints and the pubic symphysis in place begin to soften and stretch. This is accompanied by a shift in the center of gravity which may affect balance and posture.

Cramps can be felt in the 2nd and 3rd trimesters (Braxton Hicks contractions) which are muscle contractions that are irregular and cause discomfort but are harmless and are a way of preparing for true labor (Raines and Cooper, 2017).

Pregnancy complications

During pregnancy, serious health problems may arise. Complications that involve the mother's health, the fetus's health, or both need to be addressed and they include the following.

Ectopic Pregnancy – When a fertilized egg grows outside of the uterus (over 90% occur in a fallopian tube). The incidence of ectopic pregnancy is 1% and some resolve spontaneously however it can be life-threatening and requires surgery (Varma and Gupta 2012).

Incompetent cervix – Weakened cervical tissue can lead to premature delivery.

Age-related complications – Advanced maternal age (>35) is associated with a variety of complications such as miscarriage, chromosomal abnormalities, fetal growth restriction, preterm labor, preeclampsia, and gestational diabetes mellitus (Frick 2021).

Placenta accreta – The placenta attaches too deeply into the uterine lining and does not separate easily following delivery. This may cause life-threatening bleeding and/or lead to premature delivery.

Placenta previa – Abnormal implantation of the placenta over the internal cervical os. It can result in premature delivery.

Preeclampsia – Hypertension that usually occurs in the third trimester. Up to 20% of women with preeclampsia have life-threatening complications (Magee, Nicolaides, and von Dadelszen 2022).

Gestational diabetes mellitus (GDM) – Glucose intolerance with onset during pregnancy, is observed in 7% of pregnancies and increases the risk of fetal death during the last 4-8 weeks of gestation (ADA, 2004). Placental overgrowth is associated with GDM.

Uterus didelphys – A woman with two uteri. This is a congenital condition that occurs on rare occasions during embryonic development due to the "complete duplication of uterine horns, cervix, and very often also the vagina…Most women with a uterus didelphys are asymptomatic" (Ćwiertnia et al. 2022). However, the condition does increase the risk of "adverse pregnancy outcomes" such as preterm labor, breech delivery, miscarriage, and decreased live births (Slavchev et al. 2020).

Miscarriage – The "most common serious pregnancy complication is miscarriage" occurring in 11-20% of all clinically recognized pregnancies, the majority due to chromosomal abnormalities (Bottomley and Bourne 2009). A miscarriage is diagnosed usually by vaginal bleeding and the passage of products of conception vaginally.

All pregnancies carry risks however according to the NICHD the designation of "high-risk" pregnancy is for women with the following factors:

- Preexisting health conditions (e.g. diabetic or HIV-positive)
- Overweight
- Multiple births (carrying more than one fetus)
- Age (under 17 or over 35)

Prenatal care

It is very common (>88% in 2021 reported by the CDC) for pregnant women to make regular visits to an OB/GYN (obstetrician/gynecologist) or family physician for prenatal care. Prenatal care includes the following: a routine physical examination (including pelvic examination) at the initial visit, maternal weight and blood pressure at all visits, fetal heart rate auscultation after 10 to 12 weeks with a Doppler monitor or after 20 weeks with a fetoscope, fundal height after 20 weeks, and fetal lie by 36 weeks. Counseling on diet and supplementation is also usually included to reduce the risks of obesity and diabetes and pass along information about folic acid in development. Whether or not prenatal care actually improves outcomes is questionable. Fiscella (1995) found no conclusive evidence to support the need for prenatal care. However, a study by Tandon et al. (2012) found a small reduction in preterm births in women receiving group prenatal care when compared with those receiving traditional care.

Prenatal diagnostic tests

Women with a family history of a genetic disorder or those considered to be in a high-risk pregnancy category may choose prenatal testing to identify potential health problems such as sickle cell anemia or disabilities such as spina bifida. Thanks to technological advancements there are a number of issues that can be diagnosed in different ways including imaging, blood tests, and chromosomal analysis.

Common diagnostic prenatal tests

- Ultrasound, Doppler, and MRI imaging – Real-time visualization of fetal anatomy to identify structural abnormalities through different non-invasive technologies (Reddy et al., 2008).

- Non-invasive prenatal testing (NIPT) – analysis of cell-free DNA (cfDNA) circulating in the mother's blood which consists of a combination of fetal and maternal components. Used to test for common autosomal aneuploidies and trisomies, sex chromosome aneuploidies, microdeletions, and duplications, and some known monogenic disorders (Kypri et al. 2022). This can be done after 10 weeks of pregnancy however costs are not typically covered by insurance.
- Amniocentesis – Direct sampling of fetal cells from the amniotic fluid around week 16 using a needle inserted through the abdomen. Cells are cultured and provide chromosomal information and neural tube defect information within 10-14 days.
- Chorionic villus sampling (CVS) – Direct sampling of placental tissue is usually done around the 12th week using a needle inserted through the abdomen or vagina. Chromosomal information is available within 10-14 days. Both amniocentesis and CVS carry a very slight risk of pregnancy loss. A report on several studies examining pregnancy loss 14 days after an amniocentesis / CVS showed 0.6% and 0.7% respectively (Mujezinovic and Alfirevic 2007).

Labor and delivery

Labor

Early labor is often marked by persistent contractions which cause the cervix to open (dilate). Dilation is measured in centimeters. How much dilation has occurred allows one to determine how far along in labor one is.

The Bishop score to determine progress

According to Wormer, Buer, and Williford (2022), the Bishop score is used by obstetricians to determine how far along a woman is in labor. This score includes dilation as well as effacement (thinning of the cervix), position, and consistency of the cervix. It also takes into account the position of the fetal head (station) in relation to the ischial spines of the maternal pelvis. A Bishop score of 8 or higher is consistent with spontaneous labor and is used to induce labor. A score of less than 6 is considered unfavorable for induction. Induction is common with over 20% of women in the United States experiencing induced labor. The length of labor varies and is unpredictable however it often shortens with subsequent births.

Obstetric examination to assess fetal lie

It is important to determine if the fetus is presenting in the breech (feet first) or cephalic (head first) position. A noninvasive way to determine the position, presentation, and engagement of the fetus in utero is known as the Leopold maneuvers typically performed by a nurse. The nurse palpates the upper abdomen, on the sides of the uterus, and above the pubic symphysis. Confirmation of the fetal lie can be made with an ultrasound.

The three stages of labor

Stage 1 – onset of labor until dilation and effacement of the cervix are completed

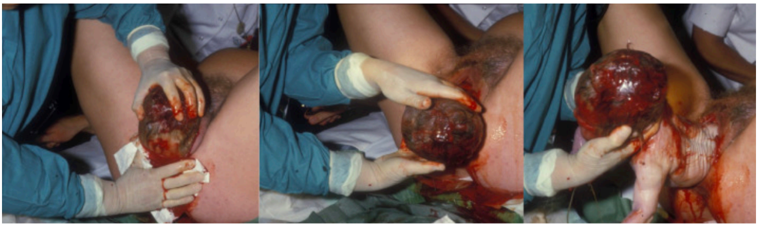
Stage 2 – time of full dilation until delivery

Stage 3 – post delivery of the infant to delivery of the placenta

Vaginal delivery

Iversen, Kahrs, and Eggebo (2021) describe the vaginal delivery process. Once the fetus begins crowning (the head becomes visible through the opening of the vagina) vaginal delivery can begin. This is often accompanied by a burning or stinging sensation. At this point the clinician or midwife will assist in the delivery. To "overcome the resistance met by the maternal bony pelvis and soft tissue" four cardinal movements happen during stage 2 of labor (pictured in the image below from Iverson, Kahrs, and Eggebo, 2021):

1. Flexion of the head = the head of the fetus is in a presentation position.
2. Internal rotation = the top of the fetal head rotates away from the ischial spines located laterally.
3. Extension of the head = the fetal head can pass the maternal pubic symphysis.
4. External rotation of the shoulders = the anterior shoulder can be delivered.



Cardinal movements during stage 2 of labor (Iverson, Kahrs, and Eggebo, 2021).

Episiotomy

An episiotomy is a small incision made in the perineum to widen the opening of the vagina. This is done to avoid tearing of the skin and assist in delivery. Stitches are required and should heal within one month after birth.

Assisted vaginal delivery

A healthcare provider may use instruments to assist in the delivery of a baby through the birth canal. It is typically employed when the natural process of labor and childbirth is not progressing as expected, or when there are concerns about the health of the mother or baby. According to O'Mahony, Hofmeyr, and Menon (2010) assisted delivery can involve 1) forceps delivery – forceps are metal instruments curved to position around the infant's head; and 2) vacuum extraction – a vacuum cup is placed on the fetal scalp and a suction device is connected to the cup to assist.

Cesarean section

When there is a failure to progress in labor cesarean section is used as an emergency measure. Typically a horizontal incision is made in the mother's abdomen and uterus. Cesarean section may be planned ahead of time under certain circumstances such as: when the mother's pelvis is too small or the fetus is too large, placenta previa, placental abruption, active herpes lesions, or previous cesarean section. An emergency cesarian section is indicated under the following conditions: fetal distress, breech presentation, shoulder presentation, and cord prolapse. Globally, from 2010-2018, over 20% of women gave birth by cesarian (Betran et al. 2021). Women in higher socioeconomic groups are more likely to choose elective cesarian even though "evidence suggests that cesarian section has a much higher risk than labor" (Singh, Pradeep, and Jauhari 2020).

Pain during labor

Fear and anxiety around the level of pain one may experience increases the chance of having a negative experience during labor and delivery (Hanna-Leena Melender 2002). Under the conditions of typical labor, a woman certainly experiences pain, however, the level of pain varies across individuals. For those electing natural childbirth, the key is preparation regarding the experiences of labor and delivery. Knowing what to expect and learning relaxation and breathing techniques help women deal with the pain. Mental preparation also helps, Duncan et al. (2017) found that preparation with mindfulness training helps women better cope with the pain, and results in greater natural childbirth satisfaction.

Analgesia and anesthesia

Labor is a unique experience for every woman. Depending on the circumstances one may not know until labor begins what approach to deal with pain will be best. There are pain relief options, analgesics reduce pain while anesthesia blocks pain:

- Nitrous Oxide (laughing gas) – inhaled, can be directly controlled by the patient to dull pain and lower anxiety.

Effects wear off quickly. For those requiring an episiotomy local infiltration with an anesthetic is used.

- Pudendal block – The pudendal nerve is a sensory and motor nerve arising from the sacral plexus and forms from the ventral spinal nerve roots S2-S4 (back of the pelvis to all the muscles, and skin in the pelvic region). To block the pudendal nerve, an anesthetic is administered either transvaginally or transperineally. It is commonly used in the case of vaginal delivery with either forceps or vacuum.
- Epidural analgesia – The most effective method for reducing labor pain is an epidural which blocks sodium channels in nerve membranes in the lower region of the body (Anim-Somuah et al. 2018). The anesthetic is administered from a catheter inserted in the spine at the L3-L4 interspace. Some risks of side effects include hypotension, bradycardia, and sedation (van Zuylen et al. 2019).

Using a certified nurse midwife

Midwives are common providers of prenatal care and birth in many countries, however in the United States it is much more common to have a hospital birth attended by an obstetrician-gynecologist. There are different types of midwives, the regulation of which is state-dependent. Certified nurse midwives (CNMs) are registered nurses who must hold a master's or higher-level nurse-midwivery degree from an accredited program (American College of Nurse Midwives, 2023). In a review conducted by Johantgen et al. (2012) births attended by CNMs compared with those attended by physicians were found to result in better maternal outcomes as well as higher breastfeeding levels. Hamlin et al., (2021) examined outcomes from 136,516 births in military hospitals and found that for both low-risk and high-risk women whose births were attended by CNMs there were improved maternal and natal outcomes. They also had lower instances of having a cesarean birth, induction/augmentation of labor, complications of birth, postpartum hemorrhage, endometritis, and preterm birth.

Planned home birth

It is impossible to predict whether or not everything will go as planned during a birth so most feel that the safest place to give birth is in a hospital. However, most births go smoothly and do not need medical intervention. Moreover, routine medical interventions in hospitals can increase the risk of negative outcomes for mothers and babies (Lothian 2014). Therefore giving birth at home may be a viable alternative. The number of women giving birth at home in the United States has increased significantly over the past few years with a peak of 1.5% observed in January 2021 (CDC, 2022). (Lang 2021) comment that planned home births, also known as community births attended by a registered nurse midwife, have benefits and risks. They recommend that planned home births be limited to low-risk pregnancies which include a single fetus in vertex presentation (head down, head first) with no previous cesarean delivery.

Planned hospital birth is strongly recommended for patients with conditions that increase the risk of maternal or neonatal adverse outcomes. A 5-year long study of Canadian women by Janssen et al. (2009) compared those who planned a hospital birth with a certified nurse midwife in attendance to those who planned a home birth and they found that the maternal outcomes were better for the women who planned a home birth compared to those who planned a physician- attended hospital birth. No significant differences between the two groups were observed for neonatal outcomes. Similarly, Hutton et al.'s (2019) meta-analysis of 500,000 home births, concluded that low-risk women who intend to give birth at home did not exhibit any increase in perinatal and neonatal mortality or morbidity compared to similarly low-risk women who gave birth in a hospital.

Postpartum

The postpartum period lasts approximately six to eight weeks after giving birth. According to the American College of Obstetricians and Gynecologists, this is " a critical period for a woman and her infant... when she is recovering from childbirth, adjusting to changing hormones, and learning to feed and care for her newborn."

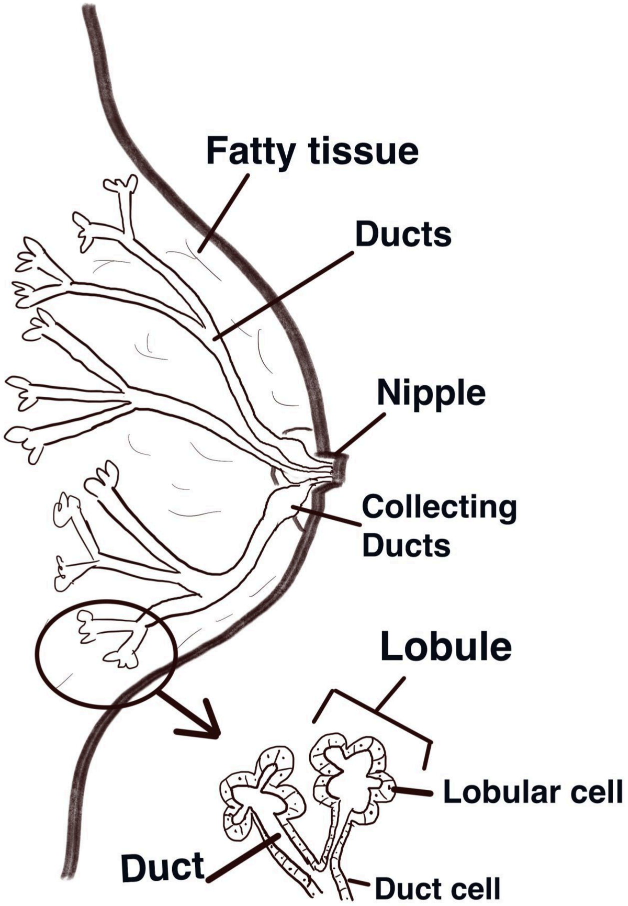
During the postpartum period, one can expect:

- Contractions, or afterpains, may last for several hours post-delivery.
- Vaginal discharge of the endometrial lining that can last for several weeks.
- Vaginal tear or episiotomy during birth can cause discomfort for a few weeks or longer.
- Incontinence can last for days or weeks due to strain put upon the pelvic floor muscles.
- Hair loss and skin changes due to a drop in progesterone.
- Moodiness and depression due to the sharp decline in progesterone and estrogen.

Postpartum depression

The term clinical postpartum depression is specifically used for depression occurring from birth until one year after. The symptoms are similar to depression such as irritability, anxiety, insomnia, wide mood swings, appetite changes, and hypersensitivity. "Postpartum depression should be distinguished from the postpartum blues, which refers to mood symptoms that are common in the first week to 10 days after delivery and that usually resolve within a few days without any intervention" (O'Hara 2009). According to Patel et al. (2012), the incidence of postpartum depression is reported as up to 15% of all new mothers. Early detection and intervention are important and treatment can be either non-pharmacological or pharmacological.

Breastfeeding


Fatty tissue
Ducts
Nipple
Collecting Ducts
Lobule
Lobular cell
Duct
Duct cell

The human mammary gland's tissue is made up of branching ducts and terminal secretory lobules. There are 15 to 20 lobes, and a lactiferous duct drains each of them. These ducts enlarge to form the lactiferous sinus before they open separately into the nipple. The milk is collected in the lactiferous sinuses and let out on the suckling of the baby. Image created by Jennifer Dever.

Humans, like all mammals, can provide infants with all the necessary nutrients directly from mammary glands located in the breast overlying the pectoralis major muscles. Mammary glands are present in both females and males but usually are functional only in the female. The adult female breast (illustrated above) contains 15 to 20 **lobes** of glandular tissue that radiate around the **nipple** and are supported by connective tissue and adipose (fatty tissue). Each lobe consists of **lobules** that contain glandular units. A **lactiferous duct** collects the milk from the lobules within each lobe and carries it to the nipple. Just before the nipple, the lactiferous duct enlarges to form a **lactiferous sinus** (ampulla), which serves as a reservoir for milk. After the sinus, the duct again narrows and each duct opens independently on the surface of the nipple.

According to the World Health Organization (WHO) early initiation of breastfeeding, within one hour of birth, protects the newborn from acquiring infection and reduces newborn mortality. This is because breast milk is how the "mother's immunological history can be transferred to her infant, to prime and stimulate the neonate's immune system as well as provide immediate immunological protection against diseases that the mother has experienced" (Power and Schulkin 2016). Notably, the maturation of the immune system is deferred in early infancy but this is "compensated by immune factors in milk" (Goldman 2002).

Breastfeeding also facilitates the emotional bonding of the mother and the baby and has a positive impact on the duration of exclusive breastfeeding. When a mother initiates breastfeeding within one hour after birth, the production of breast milk is stimulated. The yellow or golden milk produced in the first days, also called colostrum, is an important source of nutrition and immune protection for the newborn. The CDC recommends exclusive breastfeeding for the first 6 months of life, and partial breastfeeding into the second year.

Kent (2007) provides a comprehensive review of breastmilk and breastfeeding

Breast milk is synthesized in the lactocytes that line the alveoli of the mammary gland. Blood capillaries surround the alveoli. Substrates (glucose, amino acids, fatty acids, minerals, and vitamins) diffuse from the blood to the basement membrane of the lactocytes and are used for the synthesis of milk components. These are then secreted across the apical membrane of the lactocyte into the lumen of the alveolus.

There are two stages of milk secretion. **Lactogenesis I** is the stage in which the mammary glands develop the ability to secrete milk components during the second trimester of pregnancy. **Lactogenesis II,** which is the onset of copious milk secretion, occurs soon after birth. Lactogenesis II requires adequate levels of prolactin, insulin, and adrenal cortisol, and is triggered by the withdrawal of circulating progesterone after birth.

Each time the baby breastfeeds, **oxytocin** is released into the circulation. **Prolactin** plays a role in the control of the amount of milk produced. Measurement of breast volume before and after each breastfeeding for 24 hours has shown that babies will normally drain the breast one or more times each day, but do not drain the breast at each feeding. Because babies feed according to appetite, the mother's milk production is regulated to match the baby's milk intake. Current recommendations are to feed babies "on demand", therefore, there is no prescribed pattern for breastfeeding babies.

The WHO recommends **exclusive breastfeeding for the first 6 months of life**, and partial breastfeeding into the second year. However, breastfeeding does not always go smoothly and oftentimes women stop within eight weeks (Field et al. 2020). There can be difficulty in an infant latching on, nipples can become wounded and the suckling can be very painful. Feenstra et al. (2018) surveyed over 1,400 mothers who reported that "up to 40% had experienced early breastfeeding problems…including for many mothers…them being in doubt" of whether or not they will be able to provide enough nutrients for their babies through breastfeeding. Disturbing evidence links exposure to forever chemicals, known as PFAS (per- and polyfluoroalkyl substances), to mothers ending breastfeeding prior to six months (Romano et al., 2024).

Evolution of mammary glands

Power and Schulkin (2016) define milk as "a glandular secretion produced by mammalian mothers to feed to their offspring." All mammalian species (monotremes, marsupials, and eutherians) have milk that is composed of the same ingredients: water, sugars, fats, proteins, vitamins, and minerals. Mammary glands arise from a localized thickening of the epidermis and are made up of epithelial cells organized into alveoli to function as secreting tissue (Boutinaud, Guinard-Flament, and Jammes 2004). In eutherians "lactation is a staggeringly complex phenomenon involving morphological, physiological, biochemical, ecological, and behavioral adaptations" (Farkaš 2015) yet this mechanism appears to have originated long ago. Fossil evidence suggests early **mammaliaformes** (the last common ancestor to mammals), existing over 200 million years ago, produced a nutrient-rich milk-like secretion (Capuco and Akers 2009). Oftedal (2012) proposes an origin of lactation occurring within the recent mammalian ancestors more than 300 million years ago from an ancestral apocrine structure associated with hair follicles. These are potential precursors to mammary glands because they were likely present in early mammals and primitive apocrine glands "resemble mammary glands in being able to synthesize and secrete lipids and other complex organic molecules." The apocrine-hair association is observed in monotreme mammary glands presumably providing "moisture and other constituents to permeable eggs" (Farkaš, 2015). Apocrine glands are a type of sweat gland connected to the epithelium and originate from the hair germ (Best and Kamilar, 2018). In mammals, "evidence is consistent with the hypothesis that mammary glands developed from an apocrine-like gland that had an association with hair follicles and sebaceous glands" (Oftedal, 2012).

Mammary glands, an advantage over reptiles?

The ability to produce milk and lactate appears to be a significant adaptation acting first as an "egg-bathing fluid" and ultimately evolving into the "primary source of nutrients for rapidly growing altricial young" (Oftedal, 2002). Two important factors were likely under selection, nutrients provided by milk and protection from the addition of antimicrobial agents within secretions (Capuco and Akers, 2009). Vorbach, Capecchi, and Penninger (2006) argue that lactation primarily "evolved as an inflammatory response to tissue damage and infection." They cite the existence of two conserved antimicrobial enzymes, Xanthine oxidoreductase (XOR) and lysozyme involved in lactation as being the key reason for the evolution of the mechanism, with additional nutritional roles evolving afterward. XOR plays an integral part in the innate immune system along with lysozyme which comes from a gene that has been duplicated, resulting in α-lactalbumin, an important whey protein found in milk and is involved in lactose synthesis. The α-lactalbumin predates the evolution of mammals, suggesting that "the capacity to produce lactose was an ancient trait that preceded its utility in milk synthesis" (Capuco and Akers, 2009). Whatever the original selective force, clearly the adaptation of lactation allowed our ancestors to "escape the Permian-Triassic extinction...at the end of the Cretaceous" finally becoming, arguably, the dominant land vertebrates of today" (Power and Schulkin, 2016).

Think, Pair, Share

Capacitation is referred to as a “defrosting” process for sperm. Is that an apt term and why do you think this process happens?

Embryo, fetus, and infant are not interchangeable terms. Why are they often confused?

Discuss why determining whether or not one is pregnant is so important during the first five weeks of pregnancy.

Under what circumstances might a woman want to have prenatal testing done?

What arguments can be made in support of the evolution of mammary glands as being the result of a combination of factors?

Deeper thoughts

A woman can reliably determine whether or not she is pregnant using an over-the-counter test and pregnancy can be confirmed approximately three days after a missed period however almost all physicians make patients wait until 12 weeks to perform an ultrasound. What might be the reasoning for this?

What reasons might there be for the high infant and maternal mortality rates still experienced in the United States?

What might societal pressures have to do with prenatal care and whether or not a woman chooses to use anesthesia during labor?

Breastfeeding can be difficult. How might the pressure to breastfeed be connected to postpartum depression and what might be done to alleviate such pressure?

Key Terms

Acrosomal reaction

Allantois

Amniocentesis

Amnion

Amniotic fluid

Blastocyst
Capacitation
Cesarian section
Chorion
Chorionic villi biopsy
Colostrum
Cytotrophoblast
Ectoderm
Ectopic pregnancy
Egg activation
Embryo
Endoderm
Endometrium
Episiotomy
Fallopian tube
Fetus
Gastrula
Gastrulation
Gestational diabetes
Human chorionic gonadotropin
Implantation
Inner cell mass
Intrauterine insemination
Mammary gland
Mesoderm
Miscarriage
Morphogenic determinants

- Morula
- Neonatal
- Oviduct
- Placenta
- Placenta previa
- Postpartum depression
- Preeclampsia
- Preterm
- Prostaglandin
- Polyspermy
- Syncytiotrophoblast
- Trophoblast
- Yolk sac
- Zona pellucida
- Zygote

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Suggested Reading

"What to Expect When You're Expecting" by Heidi Murkoff and Sharon Mazel – This classic pregnancy guide offers week-by-week information on fetal development, changes in the mother's body, and practical advice for a healthy pregnancy.

"Mayo Clinic Guide to a Healthy Pregnancy" by the Mayo

Clinic – Written by a team of healthcare experts, this comprehensive guide covers every aspect of pregnancy, from conception to childbirth, and provides evidence-based advice.

"The Expectant Father: The Ultimate Guide for Dads-to-Be" by Armin A. Brott and Jennifer Ash – Geared towards expectant fathers, this book offers insights into the emotional and practical aspects of pregnancy and fatherhood.

"Ina May's Guide to Childbirth" by Ina May Gaskin – Midwife Ina May Gaskin shares her extensive experience in natural childbirth, offering a reassuring and informative perspective on labor and delivery.

"The Birth Partner: A Complete Guide to Childbirth for Dads, Partners, Doulas, and All Other Labor Companions" by Penny Simkin – This book is a valuable resource for birth partners and support persons, providing practical advice on how to assist and comfort the laboring mother.

"The Pregnancy Book: Month-by-Month, Everything You Need to Know from America's Baby Experts" by William Sears, M.D., and Martha Sears, R.N. – The Sears family, known for their attachment parenting philosophy, provides a month-by-month guide to pregnancy, focusing on a holistic approach to prenatal care.

Interesting Podcast

Is it normal? The Pregnancy Podcast with Jesse Ware
Breastfeeding

9.

INFERTILITY AND ARTIFICIAL REPRODUCTIVE TECHNOLOGY

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Define infertility
- Recall the female causes and male causes of infertility
- Describe how female factors are diagnosed
- Discuss treatments for female infertility
- Explain the different types of ART
- Define stratified reproduction
- Discuss the ethical issues surrounding ART

Infertility is a disease

Young women typically fear getting pregnant although most do not understand fertility and "often overestimate the chances of pregnancy" (Bunting, Tsibulsky, and Boivin 2013). According to the World Health Organization, approximately 18% of the adult population experience infertility, classically defined as "a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse" (WHO, 2023). Infertility can be subdivided into primary and secondary infertility. Primary infertility is the inability to conceive, meaning a person has never been able to get pregnant and give birth. Secondary infertility refers to those who have gotten pregnant and given birth at least once in the past. Secondary infertility is the most common form of infertility experienced by women (Vander Borght and Wyns 2018). Described as a long-lasting and complex life crisis, infertility patients report experiencing distress, depression, anxiety and decreased quality of life (Rooney and Domar 2018). Infertility ranks as one of the greatest sources of stress in a woman's life comparable to cancer (Baram et al. 1988). Jennings (2010) interviewed several women struggling with infertility and one comment from a woman named Nancy stood out:

> …a lot of women they grow up and they play with their baby dolls and they always have that. They take that for granted, that it [becoming a mother] will always be there and when it's not, it's the most life-changing thing that I think a woman can go through…

There is a falsely perceived connection between a woman's sense of herself as a woman and her body's "failure" of not being able to give birth (Poddar, Sanyal, and Mukherjee 2014). Despite the prevalence of infertility, most infertile women "do not share their story with family or friends, thus increasing their psychological vulnerability" (Rooney and Domar 2018), likely due to an internalized feeling of inadequacy. Loftus and Andriot (2012) interviewed 40 infertile women and one common theme they found was that these women could not see themselves as complete women. They believed that they had failed to achieve the goal of motherhood and "interactions with other women only add to their pain by highlighting their inability."

What causes infertility?

Infertility is a multifaceted disease linked to both singular and combined female and male factors. In approximately 50% of heterosexual couples female factors are responsible, and in 20% male factors are responsible, however for a significant percentage, there is no clear cause (Shreffler, Greil, and McQuillan 2017). Unexplained infertility is diagnosed when standard investigations fail to reveal any obvious barrier to conception (Maheshwari, Hamilton, and Bhattacharya 2008).

Female factors of infertility

- Age is the single most important female factor. This is because the ovarian reserve becomes depleted over time. Between the ages of 18 and 26 years, women experience a peak in fertility, this begins to decline after age 27 and drops significantly after 35 (Dunson, Colombo, and Baird 2002). Women in industrialized and high-income countries like the United States are delaying childbirth. According to the 2020 United States National Survey, the average age at first birth increased to 27 years (Martin, Hamilton, and Osterman 2021). This is a significant jump when compared to the 1970s when the age at first birth was 21 years old (Matthews and Hamilton 2002). This tracks with changing gender norms, with an increased emphasis on post-secondary education and career development for women. Women also may be delaying childbearing due to economic factors or partner issues.

- Underlying medical conditions that may damage the fallopian tubes, and interfere with ovulation or fertilization can cause infertility such as:
    - adhesions caused by pelvic inflammatory disease (PID) or prior pelvic surgery
    - endometriosis
    - polycystic ovarian syndrome
    - premature ovarian failure
    - uterine fibroids
    - cervical problems (structural abnormalities and or abnormal cervical mucus production
- Diagnosis of these underlying conditions is made from an evaluation of the woman's medical history, physical examination, and various imaging techniques for examining the uterus and fallopian tubes. According to Panchal and Nagori (2014) imaging techniques include: ultrasound (particularly saline-infusion sonohysterography),

hysterosalpingography (visualization of the Fallopian tubes), hysteroscopy (visualization of the uterus), and laparoscopy (visualization of the pelvic organs). Magnetic resonance imaging (MRI) is the imaging study of choice as it can detect tumors as small as 3-5 mm. Combinations of these imaging procedures may be used to confirm diagnoses.

- Factors that impact the HPG (hypothalamus-pituitary-gonad) axis:
    - disorders of the endocrine system causing imbalances of reproductive hormones
    - excessive weight gain or excessive weight loss can impact estrogen levels

Diagnosis of HPG problems is made from an evaluation of the woman's medical history, physical examination, tracking of the menstrual cycle, measuring basal body temperature, monitoring cervical mucus, measuring mid-luteal progesterone levels, progestin challenge test to demonstrate edometrium’s ability to respond, and an endocrine evaluation (Koroma and Stewart 2012).

- Exposure to environmental stressors can cause infertility:
    - alcohol consumption
    - smoking
    - STIs (sexually transmitted infections) are a leading cause of infertility: PID can be caused by Chlamydia trachomatis and Gonorrheae that can result in abscess formation, adhesions, scarring, tubal blockade, tubal damage, ectopic pregnancy
    - chemotherapy cancer treatment
    - exposure to endocrine-disrupting chemical compounds
    - emotional stress

Male factors of infertility

Babakhanzadeh et al. (2020) report the following factors responsible for male infertility:

- Physical obstruction of the tract impacts ejaculation and or impairment of sperm. Caused by:
    - STIs such as gonorrhea and chlamydia can lead to obstruction in the epididymis
    - enlargement of sperm vessels (varicocele) in the scrotum
- Factors that impact the HPG (hypothalamus-pituitary-gonad) axis:
    - disorders of the endocrine system causing imbalances of reproductive hormones
- Exposure to environmental stressors that impact sperm production and quality
    - alcohol consumption and smoking
    - obesity
    - chemotherapy cancer treatment
    - endocrine-disrupting chemical compounds
    - anabolic steroid use
    - emotional stress
- Age is also a factor in men, with fertility rates declining significantly in their mid-thirties (Dunson et al., 2002).

Diagnosis of conditions is made from an evaluation of the man’s medical history, a physical examination, and a semen analysis

How is infertility treated?

One of the first lines of treatment is to address underlying emotional stress. Domar et al. (2011) report increased pregnancy rates for those engaging in mind/body therapy. This type of practice involves meditation and relaxation. As Hajela et al. (2016) point out mind/body therapy rejuvenates the mind and clarifies thoughts helping in maintaining healthy body chemistry, and providing patience to undergo the challenge of infertility treatments.” An additional study by (Clifton et al. 2020) showed “a reduction in distress and an increase in pregnancy rates for those participating in an internet-based mind/body program as compared to those in the quasi-control wait-list group.”

Q&A with Dr. Alice Domar, Ph.D.

Associate Professor of Obstetrics, Gynecology and Reproductive Biology,

Beth Isreal Deaconess Medical Center

Dr. Alice Domar, Ph.D.

What drew you to studying different ways to help women with the stress of health-related issues, specifically infertility and IVF? Two things led me to specifically research the relationship between stress and infertility. The first was that my parents went through infertility; it took them seven years to conceive my older sister and another five to conceive me. So throughout my childhood, my mother talked about how awful it was to have infertility while all her friends and relatives were having many children. There were few treatment options back then, and zero sources of emotional support, so it was an awful time for her. The second reason is that I have always wanted to be a pioneer, to be the first at what I dedicated my career to. And no one was doing anything to relieve the distress of women with infertility. I had read an abstract of a small study that included 14 women; half received several sessions of cognitive-behavioral therapy and half did not. Four of the seven in the CBT group conceived and none of the controls did. Which sent me in the direction of applying CBT to women with infertility from a research and clinical perspective.

What have you enjoyed most about your research? I love the fact that my research is always unique and that the clinical application of what I am researching helps relieve the intense emotional pain of those struggling with infertility, as well as significantly increasing their chances of conceiving. I also appreciate the global interest in these approaches and the fact that I have the opportunity to train healthcare professionals from around the world on how to apply the clinical program to their patients.

What do you do to try to balance work with life? It is certainly easier now that my two children are in their 20's. When they were little, I didn't work full-time which did put a strain on my career goals, but I put my family first. When I went back to full-time, I always worked from home two days/week. That way I could walk them to school in the mornings. I tried to take my family with me on as many work trips as I could. I also wanted to be a good role model for my daughters, to demonstrate that a woman could have a busy and fulfilling career. Now I take long walks during the day when I don't have meetings, my husband comes with me on as many work trips as possible, and I try to minimize evening and weekend commitments.

What advice do you have for women who want a career in science? Go for it! No matter what anyone may have said to you, women are just as capable in the sciences as men are. Follow your talents and passion. Don't listen to others, listen to your own gut feeling. Find a mentor who believes in you. I had a college professor who had a massive impact on my career- he truly believed in me. It was his idea that I go into health psychology instead of medicine and it was exactly the right career path for me.

When an underlying cause is identified it is then directly treated when possible. For example, a woman with an ovulatory disorder may be prescribed clomiphene citrate (**Clomid**), an antiestrogen that competitively binds to ERs resulting in increased GnRH; or **Pergonol** (purified FSH-LH) to induce ovulation (Lindsay and Vitrikas 2015). If no cause has been identified, the first line of treatment for heterosexual couples is counseling on the timing and position of intercourse with improvements in coital practice by having intercourse every two days during ovulation. Over-the-counter urinary luteinizing hormone kits can be used to indicate the midcycle luteinizing hormone surge that precedes ovulation by one to two days.

Intrauterine insemination **(IUI)** can be utilized when there are sperm motility issues or cervical issues. This is the placement of sperm directly into the woman's uterus using a thin catheter or syringe, near the time of ovulation, to facilitate fertilization. Oftentimes ovulation will be stimulated as discussed above, then ultrasonography is performed to enable the visualization of follicular development to the point of ovulation. The mature follicles typically measure from 17 to 25 mm in average inner dimension.

The optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole was found to be in the 23–28 mm range (Palatnik et al. 2012). If another year passes without pregnancy, those with unexplained infertility may choose Artificial Reproductive Technology.

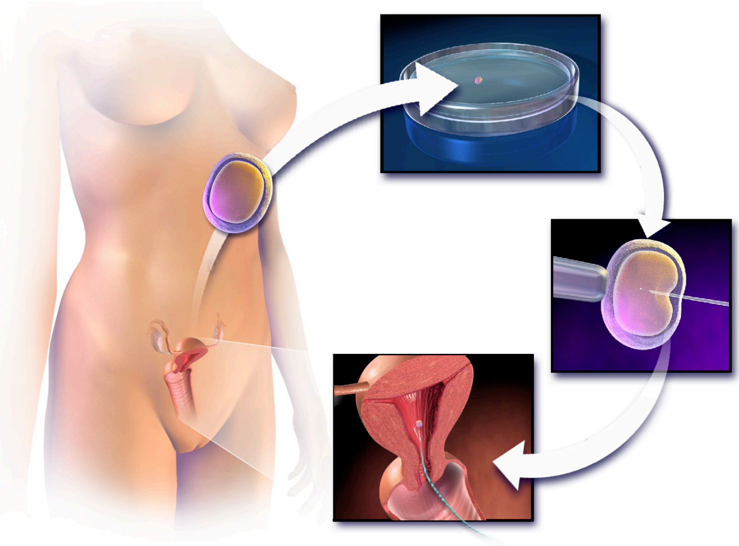
Artificial Reproductive Technology (ART)

On July 25th, 2023, the world celebrated the 45th anniversary of the birth of the first 'test-tube baby', bringing in the new age of ART (Steptoe and Edwards 1978). Since then significant advancements have been made in ART such as the development of the EmbryoScope, an embryo incubator with time-lapse imaging (Sciorio, Thong, and Pickering 2018). ART is a broad term used to describe fertility treatments in which either eggs or embryos are handled. "In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman" (CDC website on ART). ART can be costly, consuming, and highly stressful. The risk of miscarriage increases significantly for infertile women undergoing assisted reproduction (Agenor and Bhattacharya 2015).

Common ART procedures

In vitro fertilization (IVF) – the fertilization of eggs and sperm outside the body in a laboratory dish. IVF involves "controlled ovarian stimulation, oocyte retrieval under ultrasound guidance, insemination, embryo culture, and transcervical replacement of embryos at cleavage or blastocyst stage" (Pandian, Gibreel, and Bhattacharya 2015). The resulting embryos are then implanted into the woman's uterus. There is an elevated risk of multiple pregnancies with IVF which threatens the health of both mother and fetus. A joint committee opinion from the American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology strongly recommends limiting the number of embryos implanted per cycle based on age (one for those under the age of 37, three for those aged 38-40 and four for those over the age of 41 years) (2017). According to the CDC's 2020 Fertility Clinic Success Rates Report, the likelihood of a live birth from IVF is 23%. The outcome is dependent on many factors such as the mother's age, those between 20 – 30 years of age have the best IVF outcomes, (Yan et al. 2012), and whether or not frozen or fresh embryos are used, Zargar et al. (2021) report a significant increase in live birth rates when frozen embryos are used.

Intracytoplasmic sperm injection (ICSI) – a single sperm cell is injected directly into an egg to facilitate fertilization in a dish. This technique is often used when there are male infertility issues (poor sperm motility) or in cases of low oocyte yields (Palermo et al. 2017). See the image below.



Schematic image of intracytoplasmic sperm injection during IVF.

Gamete intrafallopian transfer (GIFT) – the direct transfer of both sperm and eggs into the woman's fallopian tube allowing fertilization to occur within the body (in vivo) (Asch et al. 1986). Multiple eggs are collected thanks to artificial follicular stimulation and then mixed with treated sperm. The combined gametes are placed in the fallopian tube using laparoscopy.

Zygote intrafallopian transfer (ZIFT) is similar to GIFT as ZIFT involves the transfer of a fertilized embryo (zygote) into the fallopian tube. Weissman et al. (2013) demonstrated increased success over IVF using ZIFT, attributing the success to the fallopian tube participating in key functions involved in fertilization and embryogenesis. However, traditional GIFT and ZIFT are not commonly used because they require anesthesia and laparoscopic surgery, but recent advancements in noninvasive micro-robotic GIFT/ZIFT using nano techniques have the potential to improve outcomes (Nauber et al. 2023).

Gestational Surrogacy with IVF – eggs from a donor are fertilized through IVF, and the embryos are implanted in a surrogate mother (not genetically related), also known as a gestational carrier, that will carry and give birth to a baby on behalf of another individual or couple.

How many people use ART in the United States?

The latest statistics provided by the CDC are from 2020 (Sunderam et al. 2020) in which a total of 203,119 ART procedures were undertaken (range: 196 in Alaska to 26,028 in California). This resulted in 73,831 live-birth deliveries and 81,478 infants born (range: 84 in Wyoming to 10,620 in California), representing 2% of all infants born. While ART may be an answer to infertility, it does continue to focus on the infertility of heterosexual couples, and some find that it discourages viable alternatives like child-free living and adoption.

What does the future of ART look like?

While there has been a steady increase in the age of infertile women seeking ART over the past twenty years, proactive fertility care is the new trend (van de Wiel 2022). More and more women are seeking to avoid future infertility by using planned oocyte cryopreservation however in 2018 the Ethics Committee of the American Society for Reproductive Medicine strongly recommended that women "are informed about its efficacy, safety, benefits, and risks, including the unknown long-term health effects for offspring". The recently established Prelude Fertility Network company (initiated with $200 million in start-up funding), is an example of this shift in which individuals embrace ART at younger ages (Gleicher, Kushnir, and Barad 2019). It is a company "focused on proactive fertility care to improve people's chances of having healthy babies when they're ready" in a four-step process: fertility preservation through freezing of oocytes and sperm at peak fertility (ages 20s to early 30s); embryo creation in the laboratory when the time has come to start a family, and the embryos undergo genetic screening before transfer.

Socioeconomic status, race, and sexuality impact infertility treatment

It is very important to stress that all individuals and couples should have the right to decide the number, timing, and spacing of their children, and as such addressing infertility is an "important part of realizing the right of individuals and couples to found a family" (WHO, 2023). Globally, the WHO recognizes that "inequities and disparities in access to fertility care services adversely affect the poor, unmarried, uneducated, unemployed and other marginalized populations." In the United States, Dongarwar et al. (2022) found that non-Hispanic Black and Hispanic women were approximately 70% less likely to utilize any form of infertility treatment. There are several sociodemographic factors contributing to this disparity. Black women report incidences of racism at IVF clinics while attempting to conceive using ART (Davis 2020) and they have lower IVF success rates when compared to White women (Seifer, Sharara, and Jain 2022).

Additionally, women and couples of lower socioeconomic status in all racial groups are having a difficult time overcoming the financial barriers to treatment. For example, the average cost of a single cycle of IVF (ovarian stimulation, egg retrieval, and embryo transfer) ranges from $15,000 to $30,000 (Forbes, 2023). In the United States, over 14% of the adult population age 19-44 lack health care insurance altogether and more often than not, fertility services are not covered by public or private insurers. Furthermore, homosexual couples and unpartnered individuals often encounter discriminatory practices, being denied health insurance coverage for fertility treatments granted to their heterosexual counterparts. Of note is a recent class action lawsuit filed in a Federal New York court by a lesbian couple (Goidel and Caplan) who claim "Aetna Inc. has a discriminatory health insurance policy that, on its face, engages in sex discrimination by denying LGBTQ (lesbian, gay, bisexual, transgender, queer, intersex, or non-binary) individuals equal access to fertility treatment" (Goidel v. Aetna Inc.).

This creates a "stratified" state of reproduction whereby privileged individuals fortunate enough to be able to afford ART are empowered compared to those in lower income brackets (Greil, McQuillan, and Slauson-Blevins 2011). Furthermore, this has caused some in the US to engage in 'reproductive tourism' traveling to other cheaper countries which often lack safety regulations and engage in questionable practices (Deonandan, 2015).

Think, Pair, Share

In your own words discuss why the general population has limited knowledge regarding infertility.

Why might women find infertility to be as stressful as having cancer?

Although male factors can cause infertility as much as female factors, why is there a greater focus on women when it comes to causes of infertility?

Oocyte cryopreservation may have potential repercussions for future children and for mothers who choose pregnancy at older age. What are they?

Deeper Questions

What are the pros and cons of including ART in medical insurance coverage?

What ethical implications are there regarding "proactive fertility" centers?

For some infertile women, ART can "transform infertility from a private pain to a public, prolonged crisis" (Whiteford and Gonzalez 1995). What societal changes need to happen to mitigate the discomfort women feel surrounding this experience?

International surrogacy, the act of infertile clients traveling internationally to engage the paid services of foreign surrogates to carry their babies to term, has some unique ethical challenges. How might they be overcome?

Key Terms

- ART
- Gestational surrogacy
- ICSI
- IUI
- IVF
- Primary infertility
- Proactive fertility care
- Reproductive tourism
- Secondary infertility

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Suggested Reading

"It Starts with the Egg: How the Science of Egg Quality Can Help You Get Pregnant Naturally, Prevent Miscarriage, and Improve Your Odds in IVF" by Rebecca Fett – Rebecca Fett discusses the role of egg quality in fertility and offers evidence-based recommendations to improve natural conception and IVF success rates.

"Inconceivable: A Woman's Triumph over Despair and Statistics" by Julia Indichova – Julia Indichova shares her personal journey of overcoming infertility through holistic approaches and provides hope and inspiration to others facing similar challenges.

"The Whole Life Fertility Plan: Understanding What Affects Your Fertility to Help You Get Pregnant When You Want To" by Kyra Phillips and Jamie Grifo – This book explores the various factors that can impact fertility and offers guidance on lifestyle changes to enhance fertility.

"IVF: A Patient's Guide" by Rebecca Matthews and Dan

Nayot – Written by a fertility specialist and a patient, this book provides a comprehensive overview of the IVF process, including what to expect and how to prepare.

"Not Broken: An Approachable Guide to Miscarriage and Recurrent Pregnancy Loss" by Lora Shahine – Lora Shahine, a reproductive endocrinologist, offers insights into miscarriage and recurrent pregnancy loss, including causes, treatment options, and emotional support.

"Conquering Infertility: Dr. Alice Domar's Mind/Body Guide to Enhancing Fertility and Coping with Infertility" by Alice D. Domar and Alice Lesch Kelly – Dr. Alice Domar, a renowned expert in mind-body medicine, guides managing stress and using relaxation techniques to enhance fertility.

Interesting Podcast

The Future Conceived The impacts of IVF and other Assisted Reproductive Technologies (ART) on human reproduction with Dr Rebecca Krisher

10.

WOMEN'S HEALTH

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Discuss the challenges that still lie ahead for women in medicine
- Recall the areas of inequity in medicine between male and female physicians
- Identify gender and racial gaps that still exist in healthcare
- Analyze the ways women are different than men when it comes to health
- Evaluate the impact of criminalizing abortion on women’s healthcare
- Describe the pelvic exam and explain its usefulness
- Explain the different types of reproductive tract infections
- Recall the methods used to treat the different RTIs

A perspective on women's healthcare

Dr. Elizabeth Blackwell, MD. Image from U.S. National Library of Medicine.

Known as the "field of health and healing" (Medical News Today, 2018) medicine is essential to individual and public well-being and has far-reaching social, economic, and global implications. From the beginning of the modern era onward, inequity in medicine has been the rule rather than the exception. "Historically, most medical research was conducted in men and the findings from such studies were assumed to be equally applicable to women. Sex differences and gender disparities in health and disease have therefore long been unknown and/or ignored" (Peters et al. 2016). The first bona fide female physician (with a medical degree from a U.S. medical school) was **Elizabeth Blackwell**, pictured on the ight. She graduated first in her class yet was unable to practice medicine in the same manner as her male counterparts.

Born in England in 1821 and later emigrating to Ohio, Elizabeth Blackwell states in her diary (1914) that she was inspired to become a physician by a friend suffering from a chronic illness who had encouraged her by saying “why not study medicine? If I could have been treated by a lady doctor, my worst sufferings would have been spared me”. Medical school seemed an impossible goal but Blackwell was steadfast, she wrote in her journal that “a force stronger than myself then and afterward seemed to lead me on; a purpose was before me which I must inevitably seek to accomplish”. While working as a teacher in Charleston, SC, Blackwell was able to gain access to the medical library of her employer Dr. Dickson, and applied to numerous medical schools facing rejection each time- with one reply being very clear: ‘you cannot expect us to furnish you with a stick to break our heads with’. However some were sympathetic to her desire to learn and at one point she was advised by Dr. Pankhurst, the Professor of Surgery at the medical school in Philadelphia to sneak into his lecture by dressing in “masculine attire…to watch the class”. Feeling as though this was a question of justice she did not give up her endeavor to be admitted and was finally accepted to the Geneva College in rural New York. Although she encountered discrimination, Blackwell excelled and graduated first in her class in 1849. After gaining practical experience in London and Paris, she returned to Philadelphia. Unable to gain much experience with patients in established hospitals due to misogyny Blackwell opened a small clinic to treat poor women with her sister Dr. Emily Blackwell (who had followed

Elizabeth's path, becoming the second woman to earn a medical degree in the U.S. at Case Western) and colleague Dr. Marie Zakrzewska (fellow class member of Emily at Case Western). Zakrzewska went on to establish the New England Hospital for Women and Children in Boston which became a primary training hospital for several generations of women physicians. Blackwell eventually returned to England where in 1875, she became a professor of gynecology at the new London School of Medicine for Women.

Gender imbalance in medical specialty

Dr. Blackwell was able to show that women could handle the rigor of medical school and served as an inspiration to other women. She also campaigned for better preventative care for women. Many women have followed in Blackwell's footsteps, yet women still do not have equal representation in medicine. According to the recent AAMC report (AAMC 2022), only 37% of active physicians in the U.S. are women. At leadership levels, the difference is even more stark. A 2016 study by Hofler et al. (2016) examined 950 medical school departments including the following specialties: Anesthesiology, Diagnostic Radiology, General Surgery, Internal Medicine, Neurology, Obstetrics and Gynecology, Pathology, Pediatrics, and Psychiatry found that among "all nine specialties…women comprised 13.9% of department chairs, 22.6% of vice chairs, 21.6% of division directors". The discrepancies in certain fields directly impact women's health. For instance "although cardiovascular disease is the leading cause of death among women, just 14% of cardiologists are women" (Commonwealth Fund 2023). Physicians have often failed to recognize unique aspects of heart disease in women and this has "contributed to less aggressive lifestyle and medical preventive interventions in women relative to men" (Garcia et al. 2016), and "cardiovascular disease in women remains understudied, under-recognised, underdiagnosed, and undertreated" (Vogel et al. 2021).

Discrimination and dismissiveness persist in healthcare

Over the last 200 years, medical advancements and technological innovations have drastically improved outcomes for women. Yet the differential treatment of patients based on gender, racial, and socioeconomic status persists and contributes to disparities in healthcare. Like all professions, healthcare providers exhibit implicit bias, the degree of which varies by physician race (white physicians exhibit a pro-white bias) and gender, (women show less implicit race bias than men) (Sabin et al. 2009; Sabin 2022). This bias directly leads to disparities in care (Chapman, Kaatz, and Carnes 2013). Findings from a recent survey document women having negative experiences with their healthcare provider, with nearly 30% saying physicians repeatedly dismissed their concerns and 10% reporting discrimination (Long et al. 2023).

The most common reason for a woman to be admitted to a hospital is for childbirth however maternity services in hospitals have been characterized as “disrespectful” for women and their families (WHO, 2014). Although biomedical prenatal care may reduce infant and maternal mortality rates, the intense medicalization of pregnancy can make women feel as though they are “secondary elements in the birth scenario”, subject to being controlled instead of having a needed sense of agency over their bodies (Jardim and Modena 2018). The term “obstetrics violence” recognized by the World Health Organization refers to trauma women experience during delivery and birth involving mistreatment, disrespect, abuse, negligence, and violation of human rights by health professionals. Obstetrics violence occurs both nationally and globally (Diaz-Tello 2016).

Barriers to quality healthcare

Women of color experience the poorest health outcomes of any group in the United States with shorter life expectancies, higher rates of chronic conditions, and significantly higher rates of maternal mortality (Commonwealth Fund Report, 2023). Historical policies of racial discrimination have significantly impacted BIPOC women. Iyer et al. (2022) found a strong correlation between socioeconomic and environmental factors that explain racial disparities in mortality. Chinn, Martin, and Redmond (2021) point out how the historical “treatment by the US medical establishment, particularly in gynecology, contributes to the present-day health disadvantages of Black women." Compounding this issue is the fact that there are still few physicians of color. As of 2018, only 5.8% identified as Hispanic, and 5.0% identified as Black or African American compared to 56% who identified as White (AAMC 2019). Making matters worse, on June 29, 2023, the US Supreme Court ruled in the case Students for Fair Admissions Inc. v the University of North Carolina (and the paired case against Harvard) overturning the use of affirmative action in higher education. Universities will no longer be able to consider race and ethnicity for admissions and this has the potential to significantly reduce the number of physicians of black and other minority races. The ruling will likely "increase the health inequity in underserved communities" (Montgomery Rice, Elks, and Howse 2023).

Another marginalized group in terms of healthcare is those identifying as transgender and gender-nonconforming. They often avoid seeing a doctor altogether because the experience causes so much stress. Tabaac et al. (2018) report that discriminatory attitudes and lack of knowledge create barriers to healthcare for transgender people.

Barriers to healthcare for women

- Financial – Women still earn less than men. According to the US Labor Department (US Dept. Labor 2023) “women who work full-time, year-round, are paid an average of 83.7 percent as much as men, which amounts to a difference of $10,000 per year. The gaps are even larger for many women of color and women with disabilities.” Even though the Affordable Care Act enacted in 2010 provides some form of insurance to women, many find co-payments and limited coverage as a major hindrance to care.
- Safety – One in three women report being the victim of violence and women are significantly more vulnerable to experiencing violence from a partner, known as intimate partner violence (IPV) (approximately 41% of women compared to 26% of men experience IPV, CDC Violence Prevention Website, 2022) and their inability to disclose their experience hinders their healthcare (Silva et al. 2022).

- Logistical – Women are the primary caregivers in the family and as such find the ability to schedule appointments one of the biggest challenges.
- Fear – Many women, especially those of color, avoid seeking healthcare because of a fear of the medical establishment.

Women's health has been a national priority but requires continued financial, political, and cultural support. The U.S. Department of Health and Human Services (HHS) Office on Women's Health (OWH) was established in 1991 "to improve the health of U.S. women by advancing and coordinating a comprehensive women's health agenda" ("Office of Women's Health" 2023). Since that time the OWH has helped to improve the following for women: access to health care, improved screening techniques, executed key policy changes, approved lifesaving vaccines, and issued landmark reports (Woods et al. 2015). Yet, more still needs to be done.

There are real health differences between men and women

First and foremost it is important to recognize women and men are different. Specific biological differences impact disease etiology (causes of disease) and differences in adverse drug responses. Underlying sex differences impact disease susceptibility, symptoms and progression. However, the medical community has only recently recognized that examining both sexes in both basic and clinical research is essential (Golden et al., 2017). To date, numerous health-related differences in women have been noted.

Key health-related differences in women

- Autoimmune disease (Ngo, Steyn, and McCombe 2014; Golden et al. 2017):
  - Women are significantly more impacted by autoimmune diseases than men such as Grave's disease, lupus, and Hashiomoto's thyroiditis
  - Increased immune reactivity in females might predispose them to developing autoimmune disease

    - Increased susceptibility to multiple sclerosis

- Cardiovascular Disease (Legato, Johnson, and Manson 2016; Gao et al. 2019):
    - Women have higher mortality, more symptoms, and higher rates of recurrence of atrial fibrillation
    - Women have poorer prognosis following an acute cardiovascular event
    - Women with diabetes and cardiovascular disease have a 3-fold increased risk of heart failure
- Alzheimer’s disease (Riedel et al. 2016)
    - Women develop late-onset Alzheimer’s disease more so than men, likely due to hormonal differences
- Metabolization of medication (Legato et al. 2016):
    - Variances in body size and

    distribution volumes, sex hormone levels, activity of enzymes, and effects of routes of excretion on sex-specific responses to drugs

- Depression and anxiety (Eid, Gobinath, and Galea 2019):
    - Women are more likely to present with depression and anxiety
    - Women are more likely to experience more severe symptoms

In 2001, the National Institutes of Health (NIH), the world's premier medical research organization, created a mandate requiring the inclusion of women and minorities in federally funded clinical research in "sufficient [numbers] to provide for a valid analysis of any differences … in response to drugs, therapies, and treatments." This mandate was amended in 2017 to include the requirement that recipients conducting applicable NIH-defined Phase III clinical trials ensure results of valid analyses by sex or gender, race, and/or ethnicity are submitted to ClinicalTrials.gov so that unpublished information that could reveal sex or gender/race differences will not be lost to the scientific community (NIH website).

However, Nazha et al. (2019) found that both women and ethnic minority individuals in cancer treatment clinical trials are still significantly underrepresented.

Reproductive healthcare by women has recently been limited

Women's healthcare has suffered as a result of the July 2022 Supreme Court decision on Dobbs v. Jackson Women's Health Organization that overturned Roe v. Wade, (the 1973 landmark decision that decriminalized abortion in the United States). It has led to the passage of state laws that "criminalize physicians for medical care nationally recognized as the standard of care" (Binnall 2023). Moreover, global data indicates that these laws will not necessarily stop women from seeking abortions but will certainly make them less safe (Sidik 2022). As of the 2020 census over 30 million women are living in the states where it is now illegal or effectively impossible* to access abortion, (Alabama, Arkansas, Idaho, Kentucky, Louisiana, Mississippi, Missouri, North Dakota, Oklahoma, South Dakota, Tennessee, Texas, West Virginia, Utah* and Wisconsin*). Recent MacArthur Fellow, Diana Green Foster, along with colleagues, has conducted research showing that "women denied an abortion were more likely than were women who received an abortion to experience economic hardship and insecurity lasting years (Foster et al. 2022). Those seeking assistance living in these states must travel great distances, some over 100 miles, and several states are even attempting to outlaw this travel, i.e. Idaho which recently passed House Bill 242 that forbids adults from "recruiting, harboring, or transporting" a minor seeking abortion care without parental consent. It includes obtaining abortion medication for minors" (Ehardt 2023). It is also important to remember that many women are unable to afford the travel costs now associated with accessing an abortion, not to mention the disproportionate and unequal impact abortion restrictions have on people of color, people with low incomes, LGBT individuals, and those with disabilities (Hyatt, McCoyd, and Diaz 2022).

The overturning of Roe v. Wade also has major ramifications for the quality of care that future healthcare providers can give to women patients. In many medical schools graduates will not be effectively trained in how to deal with "pregnancy complications including placental abruption, infection, ectopic pregnancy, and eclampsia because the same medications and surgical techniques utilized for abortion also treat obstetric complications" (Berg and Woods 2023). The impact from the decision is already being felt in emergency rooms in states criminalizing abortion after 6 weeks creating "clinician fear of legal ramifications when managing ectopic pregnancies" as well as hampering their ability to freely prescribe emergency contraception to survivors of sexual assault (Samuels-Kalow et al. 2022). An article published in The Guardian (McLaughlin 2023) reports that "in Idaho, doctors are leaving, looking for states where politics don't dictate how they practice medicine"… the "local hospital, announced that it would no longer provide any obstetrical care". Research shows an inverse relationship between abortion restrictions and maternal outcomes with states that restrict abortion having higher maternal mortality than states that either protect or are neutral towards abortion (Addante et al. 2021). It is important to look at the data and make informed decisions regarding how this ruling is harming women. A woman's access to the best possible healthcare depends upon the removal of structural barriers and the protection of both her and her physician's rights.

Female-specific infections

Reproductive tract infections

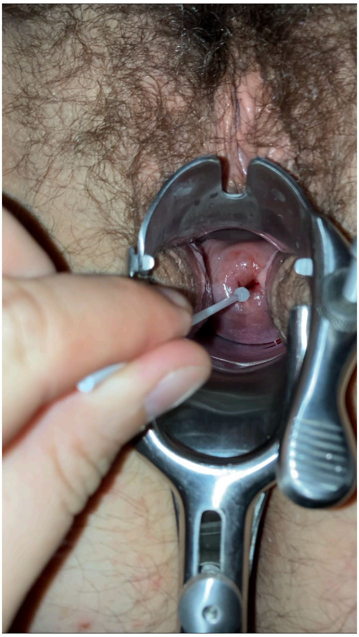
Reproductive tract infections (RTIs) are a serious issue for women that includes both non-sexually transmitted infections (non-STIs) and sexually transmitted infections (STIs) of the reproductive tract. The best way to deal with STIs is by practicing safer sex. This includes discussing past partners, history of STIs and drug use with potential partners before beginning sexual relations; using latex condoms every time (even during oral sex); and avoiding drinking alcohol or using drugs to lower the risk of participating in high-risk sex. Gynecology is the branch of physiology and medicine that deals with the functions and diseases specific to women and girls, especially those affecting the reproductive tract. Often gynecology is combined with obstetrics (a branch of medicine and surgery concerned with childbirth and the care of women giving birth). Women are encouraged to visit a gynecologist annually as part of a routine check-up and as a way to discuss day-to-day health concerns to make sure everything in their mind-body is working well together. Preventive health care is essential to minimize disease and other health problems, or screen for disease at an early stage when treatment is likely to work best.

What to expect during the annual visit (American College of Obstetricians and Gynecologists, 2023):

- talk about specific health concerns or questions
- talk about pregnancy planning or birth control
- talk about menopause and healthy aging
- pelvic exam for cervical cancer screening and a breast exam, depending on the patient's age

The pelvic exam

The pelvic exam is an uncomfortable experience and women often report being anxious and fearful beforehand, yet it is an effective way to screen for cervical cancer and sexually transmitted infections. Callahan, Caughey, and Heffner (2004) describe how the pelvic exam is performed: lying down on the examination table with knees at a 90-degree angle and the feet in stirrups (**lithotomy** position), the clinician examines the vulva.



Pap smear collection with cervical brush. Note in this photo the clinician is not wearing gloves. Clinicians are expected to wear gloves for all genital and rectal exams. Image source Mre80, Wikimedia Commons.

A **speculum**, a metal instrument that is used to widen the vagina for proper viewing and access to the cervix, is inserted and a sample from the cervix is taken by scraping the outer cervical cells (exocervix) with a scapula followed by a brush inserted into the cervical os to collect inner-cervical (endocervix) cells (see image on the left). The sample is then used to conduct a **Pap test** which checks for abnormal cells (cervical cytology screen). Cervical cancer is caused by several strains of the Human papillomavirus (HPV), discussed below, which can be detected using PCR. The following current Pap screen guidelines are from the American Cancer Society: first Pap test at age 21, followed by Pap testing every 3 years from age 25 – 65 they recommend an HPV test every 5 years.

In the past a bimanual exam (the clinician inserts gloved fingers of one hand into the vagina while pressing down on the abdomen with the other hand) was routinely conducted to feel for potential tumors however this is ineffective in screening for ovarian cancer or acute abdominal pain or vaginal bleeding, instead an ultrasound is much more effective (Qaseem et al. 2014).

Vulvovaginal candidiasis (VVC)

Vulvitis is an irritation and inflammation of the vulvar region. It may be accompanied by itching referred to as **pruritis**. There are numerous causes of vulvitis but the most common one is vulvovaginal candidiasis also known as a yeast infection, a non-STI. The fungus ***Candida albicans*** is part of the normal mucosal vaginal flora. However ***Lactobacillus*** bacterial species are considered the most common microbes found in healthy individuals, and they play an important role in keeping *C. albicans* in check (Petrova et al. 2017). Sometimes the balance is disrupted in the vaginal ecosystem causing *C. albicans* to overgrow resulting in infection. This may be due to hormonal shifts, antibiotics, or changes in the immune system and increased incidences have been noted in pregnant and premenopausal women.

The following information about the symptoms, diagnosis, and treatment of VVC is from Sobel et al. (1998). The symptoms of VVC are pruritus, soreness, a whitish discharge, painful urination, and **dyspareunia** (painful sex). Self-diagnosis is unreliable, the infection can be confirmed by the collection of a vaginal swab during a pelvic exam, the sample is viewed under a microscope followed by confirmation from vaginal culture for *C. albicans.* Over-the-counter antifungal treatment works well for uncomplicated cases. Recurrent VVC is defined as four or more episodes of proven infection during 12 months treated with judicious use of antimycotic therapy.

Bacterial vaginosis (BV)

BV affects nearly one-third of all women and is even more prevalent in Black women, it occurs when there is a shift in the predominant bacterial species in the vagina. The most common organism involved in BV is *Gardnerella vaginalis,* although the presence of *G. vaginalis* in the vagina does not always result in BV. It is often asymptomatic however BV increases the risk of some of the STIs, such as herpes simplex virus type 2 (HSV-2), HPV, HIV, and chlamydial, gonococcal, trichomonal infection, and BV is considered a risk factor for **pelvic inflammatory disease** (PID) (Chen et al. 2021).

BV is often asymptomatic however one may notice an increased vaginal discharge that has a fishy odor. BV can be diagnosed by the collection of a vaginal swab during a pelvic exam used in two different tests, the Amsel criteria and Nugent score (Colonna and Steelman 2023). The Amsel criteria involve four criteria (3 out of 4 present = confirmed BV) used to determine the presence or absence of BV which are:

1. thin, white, yellow, homogeneous discharge
2. clue cells on wet mount microscopy
3. a vaginal fluid pH of over 4.5 when placing the discharge on litmus paper
4. fishy odor released after adding 10% potassium hydroxide (KOH) solution to wet mount – also known as "whiff test"

The Nuget score test is the examination of the smear under a microscope for three bacteria morphotypes: Lactobacillus, Gardnerella, and curved gram rods. Each of these three categories receives a score based on the number of bacteria counted.

BV is treated using antibiotic oral metronidazole (500 mg twice a day for 7 days), or intravaginal metronidazole gel (5 g once a day for 5 days), or intravaginal clindamycin cream (5 g once a day for 7 days) (CDC guidelines for BV treatment).

Trichomonas vaginalis (TV)

Trichomonas vaginalis is the most common non-viral STI infectious disease. It is caused by a protozoan that infects the vulva, vagina, and urethra, and approximately 2% of all women in the United States are infected (Sutton et al. 2007). However Black women are significantly more impacted than other racial groups. Meites et al. (2015) report that "particularly high prevalences have been detected among incarcerated individuals, at 9%–32% among incarcerated women." TV is associated with infertility, the facilitation of HIV transmission, and preterm birth or low birth weight delivery (Muzny 2018).

Women are often **asymptomatic** but symptoms include profuse odorous vaginal discharge, and may also be accompanied by vulvar erythema (abnormal redness) and pruritus. Diagnosis is made from a wet prep of a vaginal swab and identification of the protozoan under the microscope where active movement of the flagella can be observed. However, according to the CDC, nucleic acid amplification tests (NAATs) are highly sensitive, detecting more T. vaginalis infections than wet-mount microscopy. Treatment involves a single high dose of oral metronidazole or a week-long course of 500 mg twice a day.

Chlamydia trachomatis

Chlamydia species are bacteria but like viruses are also obligate, intracellular pathogens. C. trachomatis is an STI and is the main cause of pelvic inflammatory disease (PID) in women. "Untreated chlamydial infection leads to PID in 20–40% of infected women" and PID is a major cause of infertility (Manavi 2006). An infected mother can infect her baby during vaginal delivery. Approximately 75% of incident infections in women are asymptomatic therefore it is difficult to determine the prevalence, however, it is estimated that 1 in 20 sexually active young women aged 14-24 years has chlamydia (Torrone, Papp, and Weinstock 2014). Like all STIs the risk of infection increases with unprotected sex (sex without a condom) and having multiple partners. Since the majority of women infected with *C. trachomatis* are asymptomatic, many remain undiagnosed.

Diagnosis of chlamydia is done by a clinician swabbing the vagina and diagnosis is based on NAATs which detect *C. trachomatis* DNA. Treatment involves a single high dose of oral metronidazole or a week-long course of 500 mg twice a day.

Neisseria gonorrhoeae

Gonorrhea is caused by the sexually transmitted obligate bacterium *Neisseria gonorrhoeae*. It is of increased concern because the pathogen "has shown an extraordinary ability to develop resistance to all antimicrobials introduced for its treatment" (Suay-García and Pérez-Gracia 2018). The incidence of gonorrhea in women in the United States has increased over the years (Learner et al. 2020). The increasing rate of infection in women is "associated with a marked increase in infections associated with injection drug use, methamphetamine use, heroin use and in sex with a person who injects drugs" (Bamberger 2020). Similar to chlamydia, most N. gonorrhoeae infections are asymptomatic in women. One reason for this is due to the site of infection which is predominantly the epithelial cells of the ectocervix (Yu et al. 2019). Left untreated infection may lead to PID and infertility among women. According to Meyer and Buder (2020), it can be diagnosed using microscopy, culture, or NAATs.

Microscopy involves swabbing a sample from the cervix and then using Gram′s staining, N. gonorrhoeae shows as Gram-negative diplococci. Culture is used to confirm biochemical and immunological testing and to determine antibiotic resistance. NAATs are the most sensitive techniques to detect *N. gonorrhoeae* however it is the most costly. The recommended treatment from the CDC as of 2022 is a single dose of 500 mg of intramuscular ceftriaxone.

Urinary tract infections (UTIs)

Urinary tract infections are the most common bacterial infections in women, especially those who are sexually active, pregnant, and post-menopausal. Post-menopausal women have higher rates of UTIs because estrogen deficiency plays an important role in the increase in uropathogenic Escherichia coli bacteria in the urine (Raz 2011; Wang et al. 2013). Typically bacteria enter through the urethra and then travel to the bladder and kidneys. As stated by Sheerin (2011) "infection of the bladder causing cystitis (inflammation) is the most common UTI" and "acute uncomplicated cystitis is the commonest form of symptomatic UTI, affecting 15% of women each year and, cumulatively, 40% of women at some point in their life (30% of these have recurrent infections)."

Women commonly present with symptoms of discomfort or pain at the urethral meatus or a burning sensation throughout the urethra, along with cystitis and or frequent urination, and incontinence. If left untreated a UTI can infect the kidneys resulting in severe damage and life-threatening sepsis (an extreme reaction by the body to infection), but most infections are less severe.

UTI diagnosis involves urinalysis and urine culture. Bates (2013) reports that the "most obvious indicator of bacterial infection in the urine is the presence of bacteria…pyuria, which is defined as urine WBC >10 or positive leukocyte esterase, indicates the presence of inflammation". Women with recurrent UTIs can correctly self-diagnose 84% of the time (Chu and Lowder 2018). Treatment of UTIs involves a course of antibiotics. The most common pathogens associated with UTIs are *Escherichia coli,* followed by *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus* and it is best to match the proper antibiotic with the infecting pathogen (Bates, 2013).

Viral Infections

Viruses are distinct from microorganisms because they are acellular (not cells) and obligate intracellular parasites (they require a host for reproduction). Additionally, most viruses are very small, generally composed of nothing more than nucleic acid surrounded by a capsid composed of proteins. Viruses are extremely diverse and have greatly influenced the evolution of cellular life (Forterre and Prangishvili 2009). New viruses, like Sars-Cov2, are constantly emerging while older ones evolve and challenge the latest advancements in treatment making them particularly difficult to combat. Those that infect the female reproductive tract discussed below are sexually transmitted therefore the best way to deal with viral STIs (like all STIs) is prevention through safer sex practices.

Humanpapilloma Virus (HPV)

HPV is sexually transmitted, spread by skin-to-skin contact, and is considered the most common viral sexually transmitted infection worldwide. HPV is highly contagious, "sexual contact with an HPV-infected individual results in a 75-percent chance of contracting the virus" (Yanofsky, Patel, and Goldenberg 2012). HPV disproportionally affects women because the cervical cells are highly susceptible to HPV infection. The virus invades cutaneous and mucosal epithelium which can be infected anywhere along the genital tract, including the vulva, vagina, cervix, and perianal regions (Yanofsky, Patel, and Goldenberg 2012). Because HPV "disrupts the mucosal integrity and immunity" HPV infection is also associated with an increase in HIV transmission (Dreyer 2018). There are over 200 types of HPV, a fraction of which are directly responsible for cervical cancer in women known as the high-risk types. They are also responsible for anal and oropharyngeal cancers, totaling 5% of cancers worldwide. The high-risk types include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, whereas low-risk types 6 and 11 are responsible for benign genital warts (de Sanjosé, Brotons, and Pavón

2018). A discussion of how HPV causes cervical cancer is found in the following Women-Specific Cancer chapter.

Symptoms and treatment of HPV

The clinical symptoms and treatments are reviewed by Yanofsky et al., (2013). Often HPV is asymptomatic, however, some types (particularly 6 and 11) do cause genital warts also known as condylomata acuminata (CA) that can be found in large clusters and may cause discomfort, burning, and pruritis. Genital warts vary in appearance and may be flat, dome-shaped, cauliflower-shaped, or pedunculated. Once infected with HPV, the virus typically requires an incubation period ranging anywhere from three weeks to eight months before any symptoms present. Studies tracking women over time have shown that within six months nearly half of all HPV infections clear up and that the great majority (>90%) clear within a few years after infection (de Sanjosé et al., 2018).

There are a variety of treatments used to remove genital warts including creams that can be administered at home (podophyllotoxin, imiquimod, and sinecatechins) or those administered by a clinician such as trichloroacetic acid (TCA) 80–90% solution. Additionally, clinicians can administer cryotherapy electrosurgery, surgical scissor excision, and laser therapy to remove warts.

The HPV vaccine

Four vaccines have been developed to prevent HPV infection, the quadrivalent (4vHPV) Gardasil, bivalent

(2vHPV) Cervarix, 9-valent (9vHPV) Gardasil-9 and the bivalent Cecolin in China (Ebrahimi et al., 2023). The vaccine Gardasil 9 (Merk) protects against HPV types 6, 11, 16, and 18. Note that this includes the two most prevalent high-risk types that cause cancer and the two most prevalent types that cause genital warts.

The CDC HPV vaccine guidelines are as follows: all children ages 11–12 years get two doses of HPV vaccine, given 6 to 12 months apart. HPV vaccines can be given starting at age 9. Some adults aged 27 through 45 years who were not already vaccinated might choose to get HPV vaccine after speaking with their doctor about their risk for new HPV infections and the possible benefits of vaccination. The FDA first approved the vaccine in 2006 and since that time it has already significantly reduced the burden of disease by preventing viral infection and transmission (Kechagias et al. 2022). However, because of costs and the lack of screening in low and middle-income countries, HPV continues to be a problem (Ebrahimi et al. 2023).

Herpes

Herpes simplex virus type 2 (HSV-2) is a sexually transmitted virus that is responsible for genital ulcers (HSV-1 causes oral infections). “HSV infection is acquired through close contact with an infected person who is shedding virus from their skin or genital secretions” (Gupta, Warren, and Wald 2007). Upon primary infection, the virus becomes latent in neural sacral ganglia therefore HSV-2 infections are lifelong with intermittent viral reactivation and shedding of viral particles from mucosal surfaces (Margolis et al. 2007; Gianella et al. 2015). Genital ulcers can be painful and cause psychological distress and like HPV the mucosal damage caused significantly increases the risk of HIV infection (Gianella et al., 2015). Pregnant women can also transmit HSV-2 to the baby at delivery which can result in central nervous system complications or death of the infant (Gupta, Warren, and Wald 2007).

Treatment of Herpes

HSV-2 cannot be cured but it can be somewhat controlled with anit-viral medication. Current antivirals such as acyclovir and famciclovir are guanosine analogs that disrupt viral DNA replication and are "effective at reducing the time to healing of recurrent and primary episodes" (Birkmann and Zimmermann 2016)

Human Immunodeficiency Virus (HIV)

HIV is sexually transmitted through genital and rectal mucosa. Left untreated, HIV causes a progressive decline in the immune system by destroying immune cells resulting in AIDS (autoimmune deficiency syndrome) the deadly disease first diagnosed in 1981. HIV is a rapidly evolving RNA virus that specifically binds the CD4 receptors on T immune cells. During vaginal intercourse, women are twice as likely to contract HIV infection from men as men are from women, and globally the vast majority of new HIV cases are due to transmission from men to women (Wira and Fahey 2008). It is thought that "intercourse-induced mechanical microabrasions of the mucosal surfaces allow HIV to directly access" immune cells (Hladik and Hope 2009).

Mother-to-infant transmission of HIV occurs at rates of 14% to 42% in various settings (Kourtis et al. 2001). According to the CDC, the incidence of HIV in the United States has declined six percent from 2015 to 2019, however, marked racial disparities exist. Only 13% of the US population identifies as Black, yet nearly 55% of all new HIV infections were reported in Black women. Disparities persist on the global level as well with half of all HIV-positive women living in eastern and southern Africa (WHO, 2023).

Treatment of HIV

No cure or vaccine has yet to be discovered for HIV and over 20 million girls and women are living with HIV (UNAIDS, 2022). Thanks to the development of multiple drugs, HIV is changing from a life-threatening infection to a long-term, manageable condition (WHO, 2023). Combination antiretroviral treatment also known as highly active antiretroviral therapy (HAART) is used to reduce viral loads to undetectable levels. This has also been an effective way to prevent pregnant women from infecting infants at birth (Bailey et al. 2018). The key to HAART is that multiple drugs are simultaneously used each with different mechanisms that block viral replication. This is done to thwart the virus' ability to evolve resistance (Shafer and Vuitton 1999). Yet the costs for HAART are very high and out-of-pocket expenditure requirements constitute a barrier for some (Assebe et al. 2020).

Prevention of HIV

There is no cure for HIV and although there have been several attempts, a successful vaccine has yet to be developed. Therefore prevention is the best option and several studies demonstrate "correct and consistent condom use can reduce HIV transmission risk by 80%" (Gursahaney et al. 2019). For individuals with a substantial risk of HIV acquisition, such as women living in a high prevalence population, or those who have intercourse without a condom, Pre-exposure prophylaxis (PrEP) is available. PrEP is the daily use of preventive antiretroviral agents by HIV-negative individuals, although "lower efficacy in risk reduction has been observed for vaginal intercourse" (Spinner et al. 2016).

Overall, reproductive tract infections are common and can be caused either by the overgrowth of microbial flora or sexual transmission of infection. They can cause discomfort, infertility, and death. The prevalence of infection varies across populations but with increased awareness and better access/ use of condoms for protection against STIs rates can continue to decline. Prevention is key.

Think, Pair, Share

What past and current social, economic, and political aspects limit women's healthcare?

How are bacterial infections different from viral infections when it comes to treatment?

What reasons might a parent give to not have their child vaccinated against HPV and how can these reasons be countered?

What factors may be contributing to the rise of some types of STIs? Propose strategies to mitigate these factors.

Deeper Questions

Recall the different disparities among Black women and RTIs. What needs to be changed to improve the health of women in general and specifically those of color?

Giving birth can be traumatic in and of itself so how is this different from obstetrics violence and in what ways can hospitals change to reduce the trauma?

Is herpes really that bad? In what ways could cultural shifts help to allay the psychological stress related to having herpes?

Many young adults are well informed about the risks of sexually transmitted diseases yet they still do not use condoms. Why?

Key Terms

Bacterial vaginosis

- Candida albicans
- Chlamydia
- Condylomata acuminata
- Dyspareunia
- Endocervix
- Exocervix
- HAART
- Herpes
- Human immunodeficiency virus
- Human papilloma virus
- Lactobacillus
- Lithotomy position
- Neisseria gonorrhoeae

Pap test
PrEP
pruritis
RTI
STI
Trichomonas vaginalis
UTI
Vulvitis

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Suggested Reading

"The Gynecological Sourcebook" by M. Sara Rosenthal –

This resource covers a wide range of women's health issues, including gynecological cancers. It provides information on prevention, early detection, treatment, and support.

"The Gynecologist's Second Opinion: The Questions and Answers You Need to Take Charge of Your Health" by William H. Parker, M.D., and Rachel L. Parker – Dr. William Parker addresses common gynecological concerns and provides valuable insights for women seeking a second opinion on their health issues.

"Reproductive Tract Infections: Global Impact and Priorities for Women's Reproductive Health" by Judith N. Wasserheit and King K. Holmes – This book provides a comprehensive overview of reproductive tract infections, their global impact, and strategies for prevention and management.

"Infections of the Female Genital Tract" by Richard L. Sweet and Ronald S. Gibbs – A textbook that covers a wide range of reproductive tract infections, including bacterial, viral, fungal, and parasitic infections, with a focus on clinical aspects and management.

"Reproductive Tract Infections and Other Gynecological Disorders: A Multidisciplinary Research Approach" edited by Shireen Jejeebhoy, Michael Koenig, Christopher Elias – This book presents a collection of research articles and studies exploring reproductive tract infections and related gynecological disorders from a multidisciplinary perspective.

"The Naked Truth" by Marvelyn Brown and Courtney E. Martin – The surprisingly hopeful story of how a straight, nonpromiscuous, everyday girl contracted HIV and how she manages to stay upbeat, inspired, and more positive about life than ever before.

"Women's Gynecologic Health" by Kerri Durnell Schuiling and Frances E. Likis – This comprehensive textbook covers a wide range of topics related to women's reproductive health, including the anatomy, physiology, and common conditions of the female reproductive tract.

Interesting Podcast

The Doctor's Art Fighting for Empowerment and Equity (with Dr. Pamela Kunz)

11.

FEMALE-SPECIFIC CANCER

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Restate the characteristics of cancer cells and explain the process of transformation
- Recall the difference between DCIS and IBC and explain the two types of IBC
- Describe how the molecular expression profile of a tumor is an important diagnostic step
- Compare the different risk factors for reproductive cancers
- Describe the different treatment options for each type of female-specific cancer
- Discuss the disparities in cancer incidence rates among women of color

Jane Cooke Wright, M.D., a Pioneer of

Chemotherapy

Dr. Jane Cooke Wright, image from the National Library of Medicine.

Research into chemotherapy led to advancements in treatment and better cancer prognoses. Dr. Jane Cooke Write was an important pioneer in the use of chemotherapy to treat cancer, noted by Crosby (2014) as "one of the first scientists to test anti-cancer drugs on humans rather than solely on mice, discovering the use of the popular antimetabolite drug methotrexate on solid tumours". Wright et al. (1957) demonstrated the efficacy of this chemotherapy agent in human cancer tumors leading to a cure for choriocarcinoma (Li et al. 1958). In a tribute to Cooke by Edith Mitchell from the American Society of Clinical Oncology (ASCO) in 2021 Wright is referred to as "The Mother of Chemotherapy." Yet, a comprehensive paper on the history of chemotherapy by DeVita and Chu published in 2008 and cited over 2,222 times, fails to mention Cooke. From her NY Times Obituary (Weber, 2013) it is clear that the omission is problematic:

Jane Cooke Wright was the first Black woman to be named associate dean of a nationally recognized medical institution, the New York Medical College in 1967, and at the time, she was the highest-ranking African American woman at a U.S. medical school. In 1949, along with her father, Dr. Louis Wright who had established the Cancer Research Center at Harlem Hospital, she started testing chemical anti-cancer agents (chemotherapy) on human leukemias and other cancers. This research led to her seminal work in 1951 which established the efficacy of methotrexate in treating breast cancer. This research laid the foundations for treating tumors with chemotherapy. She was also instrumental in using a personalized approach to cancer, recognizing that individual tumors required separate analyses and treatments. Jane Cooke Wright became director of the Cancer Research Center following her father's death in 1952. In 1955, she became an associate professor of surgical research at New York University Medical Center and was appointed to the President's Commission on Heart Disease, Cancer, and Stroke by President Lyndon B. Johnson in 1964. Wright was also a founding member of the American Society of Clinical Oncology and served on the board of directors of the American Cancer Society, New York. She published more than 100 papers throughout her career and led delegations of cancer researchers to Africa, Asia, and Eastern Europe.

Wright played a vital role in the advancement of the treatment and care and she should be recognized for her contributions. When chemotherapies were first discovered there was hope of finding a "magic bullet" to cure cancer. As Mukherjee comments in his book The Emperor of all Maladies (2010) "How many of us have asked the question, 'If this great country of ours can put a man on the moon why can't we find a cure for cancer?" A multitude of researchers have been, and are working to find a cure but "what they're learning is more of what they already learned — which is that cancers are extremely complex" (Hayden 2008). In this chapter, we will discuss the cancers that are more prevalent in females and are associated with female reproductive organs.

Cancer sucks, a brief overview of cancer

Nearly one million women in the United States received a cancer diagnosis in 2023 and over 287,700 died of the disease. Most importantly, the incidence trends are less favorable for women when compared to men (Siegel et al., 2023). Cancer is a complex genetic disease.

Six key characteristics of cancer cells have been identified (reviewed by Hanahan and Weinberg 2011)

1. dividing without limits (cell proliferation)
2. resisting cell death (anti-apoptosis)
3. inducing the formation of new blood vessels (angiogenesis)
4. resisting anti-growth signals
5. inducing growth signals
6. activating the movement of cells from the tumor that travel through the bloodstream or lymphatic system, and establishing secondary tumors in distant parts of the body (metastasis)

Benign tumors remain localized and confined in their original growth site whereas cancerous (**malignant**) tumors can spread into other tissues (**metastasize**). Cells become cancerous through a multistep process usually involving multiple mutations accumulating over time that lead to the transformation of the cell. These mutations turn proto-oncogenes into oncogenes and deactivate tumor suppressor genes and DNA repair genes. Proto-oncogenes are involved in the regulation of cell division and cell-cell contact. Tumor suppressor genes are involved in controlling programmed cell death and DNA repair genes are critical in maintaining the integrity of the genome.

Cancers often develop in progressive steps going from slightly abnormal to tumorigenic to malignant to metastatic. When cells begin to divide abnormally they are known as dysplasia. Additional mutations occur leading to these cells becoming increasingly abnormal and referred to as carcinomas in situ. In time the tumor exhibits "a high degree of genomic complexity…which…drives the evolution of tumor response or resistance to therapy" (Hurvitz et al., 2021). Once a tumor becomes malignant it can become **metastatic**.

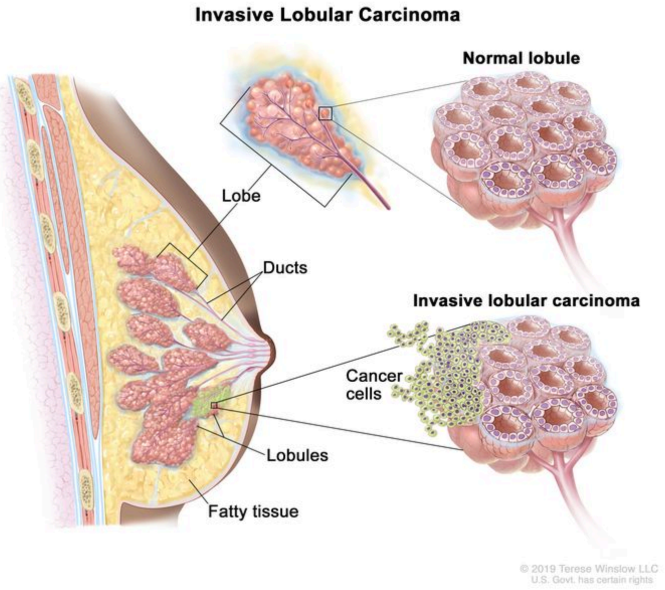
Specific types of cancer are designated by their **primary site of origin**, e.g. breast cancer starts in the breast tissue cells. Breast cancer is the most common cancer diagnosed in women in the United States whereas lung cancer is the leading cause of cancer-related deaths (Sung et al. 2021). Early diagnosis of cancer and access to effective treatments are essential for a good prognosis.

Breast cancer (BC)

Breast cancer is the most common cancer in women, impacting one out of every eight women (Siegel et al. 2023). Men also can develop breast cancer, however, this is very rare (the incidence of BC in men is 1 of 883). Thankfully, advancements in screening, diagnosis, and treatment have increased breast cancer survival rates. However, breast cancer remains a significant health issue despite advancements in screening and treatment for several reasons such as the presence of aggressive subtypes, underlying genetic factors, tumor resistance to treatment, and health disparities.

Different subtypes of BC

Like all cancers, breast cancer is a diverse and complex disease. Within the ductal-lobular unit of the breast, abnormal cells may arise resulting in lesions that can develop into atypical ductal hyperplasia and then into premalignant ductile carcinoma in situ (DCIS). DCIS, illustrated on the right, is a non-invasive type of pre-cancer with the "highly variable potential of becoming invasive however"…"studies on DCIS from non-treated patients show that many lesions, if left alone, will never progress to invasive disease" (Bergholtz et al. 2020).


Invasive Lobular Carcinoma
Normal lobule
Lobe
Ducts
Invasive lobular carcinoma
Cancer cells
Lobules
Fatty tissue

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Invasive lobular carcinoma begins in the lobules (milk glands) of the breast and spreads outside the lobules to other tissues in the breast. It can also spread through the blood and lymph systems to other parts of the body.

Invasive breast cancer (IBC) means that the cancerous cells have spread to surrounding tissue and left untreated will metastasize (image above). Invasive breast cancer may or may not arise from DCIS and symptoms may include a “swelling or lump in the breast, swelling in the armpit (lymph nodes), nipple discharge (clear or bloody), pain in the nipple, inverted (retracted) nipple, scaly or pitted skin on the nipple, persistent tenderness of the breast, and unusual breast pain or discomfort” (Sharma et al. 2010). IBC is a very diverse disease, however, two general subtypes are recognized Łukasiewicz et al. (2021):

- **invasive breast cancer of no special type (NST)**, formerly known as invasive ductal carcinoma (this is the most frequent subgroup up to 80%)
- **invasive breast cancer of special type**

Within these two groups, breast cancer is further classified by molecular expression of different receptors, growth factors, and proliferation markers associated with the tumor.

Łukasiewicz et al. (2021) report that 70% of all global breast cancer cases are ER+, whereas 10-15% are HER2-. Identification of these molecular subtypes improves outcome predictions. For example, those described as having a Luminol A category tumor (ER+ and PR+, but HER2-) have the best prognosis, followed by the Luminol B category tumor (ER+ and PR-, and HER2- with Ki67), and then Triple-Negative Breast Cancer

Molecular subtypes of BC

ER+ for the presence of estrogen receptor

PR+ for the presence of progesterone receptor

HER2+ for overexpression of

human epidermal growth factor receptor-2

Ki67 for the presence of a proliferation marker

(TNBC) also known as basal-like BC is ER-, PR-, and HER2- with the worst prognosis. TNBC constitutes about 20% of all breast cancers and is more common among women younger than 40 years of age and African-American women. There is also an association between socioeconomic status, level of education, and incidence of HER2- and TNBC subtypes relative to the less aggressive Luminal A subtype (Aoki et al. 2021).

Another key reason to identify tumors based on molecular subtype is that several treatments have been developed to directly target different molecular subtypes and patients can be spared chemotherapy in these cases (Lau, Tan, and Shi 2022).

Risk factors associated with BC

- Being female

Compared to men, women are much more vulnerable to the development of breast cancer because of hormonal differences. A positive relationship between the activity of estrogens and an increased risk of breast cancer has been documented (Aubé, Larochelle, and Ayotte 2008). Estrogen exerts stimulatory effects while androgens exert inhibitory effects regulating cell proliferation in breast cells and when this balance is disrupted progression of cancer may occur (Labrie 2006). In menopausal women taking hormone replacement therapy (HRT) with estrogen and progesterone research indicates there is an increased risk of luminal A breast cancer, however, the risk significantly decreases after two years of stopping HRT (Sun et al. 2017).

- Age

Like most cancers, the older one gets the greater the risk of developing breast cancer. Most breast cancers are diagnosed after age 50. However, where a woman lives can make a difference, women living in African and Asian countries are being diagnosed at younger ages (Kabat et al. 2017).

- Parity

Parity is carrying a pregnancy to a viable age. Fortner et al. (2019) found that greater parity is associated with a substantially lower risk of ER+ cancer but not ER- cancer and that breastfeeding duration is correlated with a lower risk of ER- cancer. Compared to nulliparous women (having never carried a pregnancy to birth), higher parity was inversely associated with luminal B breast cancer.

- Lifestyle

Alcohol consumption and an overconsumption of dietary fat intake can increase the risk of breast cancer. Alcohol consumption can elevate the level of estrogen-related hormones in the blood and trigger the estrogen receptor pathways. Research combining 20 cohort studies found a positive association between alcohol consumption and breast cancer subtypes ER+ PR+, ER+ PR-, and ER-PR- (Jung et al. 2016). Body fat may contribute to the development of breast cancer but the mechanism is unclear and an increased risk of breast cancer is correlated to high body mass index for some populations but not all (Pettersson and Tamimi 2012). Increased body size in pre-menopausal women was linked to an increased risk of developing TNBC (Turkoz et al. 2013).

- Genetics

Exposure to carcinogens (e.g. smoking) and spontaneous mutations (e.g. DNA replication error) in oncogenes and tumor suppressor genes lead to cancer. Individuals can also inherit mutations that elevate the risk of developing BC however, “8/9 women who develop breast cancer do not have an affected mother, sister, or daughter” (Collaborative Group on Hormonal Factors in Breast Cancer 2001). Numerous genes have been identified as playing a role in breast cancer development.

The most well-characterized genes associated with BC (reviewed by Sun et al., 2017):

Breast cancer associated gene 1 and 2 (BRCA1 and BRCA2) are tumor suppressor genes. The majority (approximately 80%) of breast cancers arising from BRCA1 germline mutation are TNBC.

Human epidermal growth factor receptor 2 (HER2), also known as c-erbB-2, is an important proto-oncogene in breast cancer. HER2 protein is an epidermal growth factor receptor (EGFR) form heterodimers with other ligand-bound EGFR family members such as Her3 and Her4, thus activating downstream signaling pathways

Epidermal growth factor receptor (EGFR), also known as c-erbB-1 or Her1 in humans, is a proto-oncogene that encodes the EGFR protein. This is a cell surface glycoprotein activated by ligands that trigger downstream signaling pathways. Overexpression of EGFR is found in more than 30% of cases of inflammatory breast cancer (IBC), a very aggressive subtype of breast cancer.

c-Myc is a proto-oncogene that encodes a transcription factor involved in the initiation and progression of breast cancer.

Detection and treatment of BC

Being familiar with the appearance and feel of one's breasts can help one notice changes that may be of concern. However, mammograms (an X-ray of the breast) are the best way to screen for BC. Drawbacks of mammograms include incidences of false positives and overtreatment as well as false negatives. A breast MRI is used along with mammograms to screen women who are at high risk for getting breast cancer. The United States Preventative Services Task Force (USPSTF) currently recommends that women who are ages 50 to 74 get a mammogram every two years (USPSTF, 2016) however the USFSTF is now in the process of updating these guidelines.

Molecular screening for biomarkers helps to determine which therapies are most effective. For example, ER+ status indicates the use of endocrine therapy such as Tamoxifen or an aromatase inhibitor. Tamoxifen is a selective estrogen receptor modulator (SERM) that blocks the effects of estrogen on ER+ breast cancer cells. Aromatase inhibitors block the conversion of androgen into estrogen. Anti-HER2 therapy such as Herceptin targets HER2- positive breast carcinomas.

Surgery for BC

Surgery involves the removal of the tumor and a small amount of surrounding tissue (lumpectomy / breast-conserving surgery) or the removal of the breast (mastectomy). More women are choosing a mastectomy over breast-conserving surgery. A review and meta-analysis of over 1.3

million breast cancer patients found that those receiving breast-conserving surgery experienced significantly better overall survival and breast cancer-specific survival than patients treated with mastectomy (Christiansen et al. 2022).

Radiation Therapy

Radiation therapy (RT) involves focusing radiation on the area affected by the cancer or on the whole breast.

Chemotherapy

Multiple drugs that inhibit cell division are usually prescribed in combination to minimize tumor evolution. These have side effects depending on the type, dose, and length of time given but the side effects generally abate after treatment is finished. For younger women, premature menopause may occur leading to infertility.

Treatment options depend on the progression of the disease and the molecular subtype. For DCIS the goal is to prevent these potential cells from transforming into invasive carcinoma. Studies indicate that lumpectomy combined with RT reduces DCIS recurrence (Kalwaniya et al. 2023). For IBC that has not yet spread chemotherapy is used to reduce tumor size and then surgery is performed. Whole-breast RT is generally used after breast-conserving surgery. For tumors with the triple negative molecular profile (TNBC), chemotherapy is the main treatment. Anti-HER2 therapy is paired with chemotherapy to treat HER-2+ cancers. For metastatic breast cancer, therapeutic goals are prolonging life and symptom palliation. Currently, metastatic breast cancer remains incurable in virtually all affected patients (Riggio, Varley, and Welm 2021).

Q&A with Dr. Mary-Helen Barcellos-Hoff, PhD.,

Professor and Vice Chair, Research, Wun-Kon Fu Endowed Chair in Radiation Oncology,

University of California San Francisco

Dr. Mary Helen Barcellos-Hoff, Ph.D.

What drew you to researching radiation therapy, and specifically its effect on transforming growth factor beta for cancer treatment? My graduate degree is in Experimental Pathology, which was focused on using preclinical models to understand the development of disease. My graduate research concerned the response of cancer cells to radiation and chemotherapy standard of care. using a 3-dimensional model called multicellular tumor spheroids, which stimulated my interest in cell-cell interactions and morphogenesis. To learn more about the cell biology of normal tissues, I conducted postdoctoral research investigating the regulation of milk protein production in mouse mammary epithelial cultured in 3D on an extracellular matrix (ECM). When I began my own lab, I decided to study whether radiation affected the ECM, and if that contributed to the mechanisms by which radiation increases cancer. I found that the mammary gland ECM is remodeled upon radiation exposure is reminiscent of wound healing, which I knew from my graduate program in experimental pathology is regulated by TGFbeta. Hence, I tested whether TGFbeta is a mediator of the ECM remodeling and discovered that radiation actually induces TGFbeta activity. I have since studied what TGFbeta does in irradiated tissues to promote cancer and what role it plays in the response to radiotherapy.

What do you like most about your career? I like that I choose the problems to work on and that I can follow the science where it leads me using the unique insights gained from my own experiments and my particular knowledge of the literature. I also enjoy the element of serendipity in biological research—it is so vast that one's knowledge is not just a sliver, but a self-curated sliver based on exposure and interests that generates new ideas. I like the independence, even though it comes at a high cost of insecurity because one must obtain funding and publish by subjecting to the critiques of others.

What advice do you have for future women scientists? Academic scientists must be self-motivated by curiosity but stubborn enough to prevail even when others critique their ideas. Like everyone else, scientists resist change in major paradigms, and the bar of proof is high to shift ideas. Cultural framing of how women should contribute to society is a barrier to promoting new ideas. Women scientists need to be cognizant of their own tendencies to step back and avoid conflict to reframe scientific debate in a gender-neutral fashion.

Cervical cancer

The WHO (2023) notes that globally, cervical cancer is the fourth most frequent cancer in women and it disproportionately affects those in low- and middle-income countries. The rates of cervical cancer have dropped dramatically in high-income countries thanks to regular screening via a Pap test (a medical screening test used to detect abnormal cervical cells in the cervix, which is the lower part of the uterus that opens into the vagina) and the administration of the HPV vaccine. As noted in the section on HPV, cervical cancer is caused by several types of HPV. Over time cervical cells become transformed and symptoms might include post-coital or abnormal vaginal bleeding and or pelvic pain.

Snijders et al. (2006) describe the molecular mechanism of HPV-mediated carcinogenesis. The HPV virus has two genes, E6 and E7 that encode for early proteins which inhibit tumor suppressors p53 and pRB. E6 also activates telomerase activity increasing cell proliferation. It also down-regulates the host immune response. E7 also increases genomic instability and promotes the accumulation of chromosomal abnormalities. This contributes to the transformation of the cell. E6 and E7 activation must also be combined by the accumulation of additional mutations before the cancer becomes invasive.

The progression of the disease involves interactions with HPV and cofactors. These cofactors include long-term smoking, high parity (five or more full-term pregnancies), long-term use of oral contraceptives, and HIV infection (de Sanjosé, Brotons, and Pavón 2018).

HPV prevention

Primary prevention of HPV

The introduction of HPV vaccines is instrumental in the prevention of cervical cancer and is "considered one of the most significant events in medicine and global healthcare" (Akhatova et al. 2022). The vaccines are highly effective in preventing HPV infection and diseases related to HPV infection when given to prepubertal girls and boys (Kechagias et al. 2022).

Secondary prevention

The Pap test is the original cervical screening cytological test to detect abnormal cells. However HPV-based screening using PCR is more efficacious at detecting cervical pre-cancers compared with cytology (Cohen et al. 2019).

Diagnosis and treatment of cervical cancer

Cohen et al., (2019) report that cervical examination using a colposcope (lighted magnifying instrument) allows for the viewing of abnormal lesions. A cone biopsy done under general anesthetic allows for histopathological assessment of the cervical tissue.

Surgery is the first line of treatment and the extent depends upon the progression of the disease. There are different types of surgery:

- radical hysterectomy (resection of the uterus, cervix, parametria, and cuff of the upper vagina)
- modified radical hysterectomy (less parametrium resection and a smaller vaginal cuff)
- bilateral pelvic lymphadenectomy (dissection of pelvic lymph nodes)
- radical trachelectomy (resection of the entire cervix and upper vagina and parametrium) available for younger women wishing to preserve fertility

Locally advanced cervical cancer treatment often involves chemotherapy alone or combined with radiation therapy. Chemotherapy may also be used to treat metastatic cervical cancer.

Ovarian cancer

A complex disease, ovarian cancer causes more deaths than any other cancer of the female reproductive system (CDC, 2023). Death rates are so high because effective screening strategies for the early detection of ovarian cancer do not exist and diagnosis does not occur until later stages. However, the rates of ovarian cancer diagnosis are declining likely due to the increased use of oral contraceptives that contain hormones that suppress the menstrual cycle and prevent ovulation. By reducing the number of ovulatory cycles a woman goes through during her reproductive years, oral contraceptives may lower the risk of developing certain types of ovarian cancer, particularly those that originate in the ovarian surface epithelium (Fathalla 2013).

There are two broad categories of ovarian cancer, (1) epithelial and (2) non-epithelial, each further categorized by histology (what the tissue looks like). The vast majority of ovarian cancers are in the epithelial category, non-epithelial ovarian cancers account for ~10% of ovarian cancers. Within the epithelial group, low-grade serous carcinomas (LGSCs) have a better prognosis, whereas high-grade serous carcinomas (HGSCs) account for 80% of all types of epithelial cancer (Stewart, Ralyea, and Lockwood 2019).

Risk factors for ovarian cancer

- Age

Most women with ovarian cancer are diagnosed in later life, with a median age of diagnosis of 63 years (Stewart, Ralyea, and Lockwood 2019).

- Genetics

Mutations in BRCA1 or BRCA2 tumor suppressor genes are associated with ovarian cancer. Either mutation is found in up to 17% of patients (Matulonis et al. 2016). Inheritance of a germline mutation in genes involved with DNA repair mechanisms associated with Lynch syndrome has been observed in ovarian cancers (Stewart, Ralyea, and Lockwood 2019).

- Endometriosis

Endometriosis has been associated with endometrioid and clear-cell ovarian cancer, as well as low-grade cancers but the risk differs depending on the subgroup type of endometriosis (Heidemann et al. 2014).

- HRT

Hormone replacement therapy (HRT) has been shown to increase the risk of developing ovarian cancer in postmenopausal women. However, the use of oral contraceptives in younger women has been shown to reduce the risk of developing ovarian cancer.

- Nulliparity

Women who have given birth have a reduced risk of all subtypes of ovarian cancer.

Tubal ligation and hysterectomy are associated with a reduction in the risk of developing ovarian cancer as well as the removal of one or more of the ovaries and fallopian tubes (unilateral or bilateral salpingo-oophorectomy (removal of the ovaries and the fallopian tubes) Matulonis et al., 2016).

Diagnosis and treatment of ovarian cancer

Most women are asymptomatic however some may experience abdominal bloating, abdominal and/or pelvic pain, fatigue, and shortness of breath (Matulonis et al., 2016). Gastrointestinal problems such as diarrhea, nausea, vomiting, and gastrointestinal reflux may occur. Detection involves transvaginal ultrasonography combined with a CA125 blood test. CA-125 stands for "cancer antigen 125", a glycoprotein that is a biomarker (an indicator of a condition, or response to treatment) for ovarian cancer. However (Charkhchi et al. 2020) report that "early diagnosis of ovarian cancer at stages I and II through screening with CA125 has shown little promise…but hopefully in the future combining this with other biomarkers can increase the sensitivity."

The first line of treatment includes cytoreduction (to shrink tumors) then chemotherapy followed by interval surgical cytoreduction and additional chemotherapy after surgery. Better outcomes are noted when surgery is performed by a gynecological oncologist rather than a general surgeon (Matulonis et al., 2016).

Uterine cancer

Uterine cancer is the most common gynecologic cancer and the incidence is on the rise (Lu and Broaddus 2020). There are two types of uterine cancer, endometrial cancer and uterine sarcoma. Endometrial cancer is much more common than uterine sarcoma which is found in 3-7% of uterine cancer patients (Mbatani, Olawaiye, and Prat 2018). Morice et al. (2016) provide a review of endometrial cancer noting that there are two subtypes of endometrial cancer: endometrioid and non-endometrioid. Type I, endometrioid cancer, accounts for 80% of endometrial cancers, and patients with this subtype have a good prognosis. Type I tumors are low-grade (slower-growing), estrogen-positive, diploid, and often involve the progression of precancerous cells (complex atypical hyperplasia, CAH). Whereas type II non-endometrioid tumors are high-grade (faster-growing), aneuploid, and hormone-independent, lacking precursor lesions, with a poor prognosis.

Risk factors for uterine cancer

- Obesity

Compared with other types of cancer in women, obesity is significantly more associated with endometrial cancer with over half of all endometrial cancers attributed to being overweight. This may be because after menopause adipose tissue, commonly known as fat, becomes the main site of estrogen synthesis which "acts not only as a mitogen, but also as a mutagen" (Onstad, Schmandt, and Lu 2016). Obesity is also associated with polycystic ovary syndrome, another risk factor for endometrial cancer (Barber and Franks 2021).

- Estrogen-only HRT

Unopposed estrogen increases the risk of endometrial cancer. Combined with progesterone, HRT does not pose a risk (Sjögren, Mørch, and Løkkegaard 2016).

- Tamoxifen

Tamoxifen, the breast cancer treatment that blocks estrogen receptors, actually has proestrogenic effects in the uterus, doubling the risk of both endometrioid and nonendometrioid types of endometrial cancer. When taken for more than five years the risk quadruples (O. Lavie et al. 2008).

Diagnosis and treatment of uterine cancer

The most common symptom is abnormal uterine bleeding which includes bleeding between periods or after sex or any unexpected bleeding after menopause (Henley et al. 2018). Although uterine cancer is more common in White women, racial disparity exists in the diagnosis of uterine cancer among

Black patients with Black patients not receiving guideline-recommended diagnostic procedures or experiencing delays in diagnosis compared to White patients (Xu et al. 2023). Furthermore, Henley et al. (2018) examined incidence and mortality data from 1999-2016 and they found that Black women were twice as likely to die from uterine cancer as women in other racial groups.

An endometrial biopsy is used to confirm diagnosis however if there is uncertainty, cervical dilation, and curettage is recommended (Morice et al. 2016). Initial management of endometrial cancer is surgery involving the removal of the uterus, cervix, fallopian tubes, and ovaries along with lymph-node evaluation. For younger women who wish to remain fertile, those with CAH and low-grade tumors use of progestin-containing IUDs has shown success but recurrence rates remain high (Andress et al. 2021). Lu and Broaddus, (2020) report chemoradiation therapy followed by four cycles of carboplatin and paclitaxel chemotherapy is the standard treatment for invasive cancer. However, similar to breast cancer, assessment of estrogen receptor (ER) progesterone receptor (PR), and epidermal growth factor receptor 2 (HER-2) status is now also conducted. Recent use of a combination of antihormonal and biologic agents has shown promise for second- or third-line treatment for endometrioid endometrial cancers.

The prevalence of cancer makes it a significant life-threatening disease for all. In 2022 the estimated number of new female-specific cancer cases was 402,980 and deaths were 75,080 (Siegel et al., 2022). The types and causes of cancer are very complex and as the population continues to age the burden of cancer will increase however advancements in screening and treatments make a real difference in the fight against cancer. The 20-year trend in breast cancer and ovarian cancer death rates in women is on a gradual decline, and the sharp decline in cervical cancer rates thanks to the HPV vaccine is notable. Since the 2016 launch of the Cancer Moonshot, a national effort prioritizing cancer research, over 250 research projects have been funded to improve treatments, map tumors, and expand prevention and detection (Sharpless and Singer 2021). However, disparities in the United States in prevention programs, screening, diagnosis, and treatment must also be addressed.

Think, Pair, Share

Early diagnosis of cancer is key to positive outcomes. What are some ways to improve getting people to take advantage of regular screenings early on?

How does lifestyle increase the risk of developing cancer?

What factors may be contributing to higher rates of breast and uterine cancer incidences in women of color?

How much does education level contribute to outcomes for women diagnosed with cancer?

Deeper Questions

What societal factors play into the decision a woman makes on whether or not she gets a mastectomy with reconstruction or breast-conserving surgery?

What factors can influence women of different ages to engage in preventative action to reduce their risk of cancer?

With the average price of cancer drugs doubling in the last decade, the unsustainability of drug prices is especially concerning in oncology. What can be done to make cancer treatments more affordable in the United States?

Key Terms

Benign
BRCA1 and BRCA2
Carcinogen
Carcinomas in situ
DCIS
Dysplasia
EGFR
ER+/ER-
IBC
HER2+
HGSC
HRT
LGSC
Malignancy
Metastasis
Nulliparity
Parity
PR+/PR-
Protooncogene

SERM
Tamoxifen
TNBC
Tumor suppressor gene

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Suggested Readings

“The Emperor of All Maladies: A Biography of Cancer” by Siddhartha Mukherjee – This Pulitzer Prize-winning book provides a comprehensive history of cancer research and treatment, shedding light on the broader context of cancer understanding and management.

“Radical Remission: Surviving Cancer Against All Odds” by Kelly A. Turner – This book explores cases of individuals who have experienced complete remission from cancer, including some women-specific stories. It delves into the factors that may contribute to extraordinary healing.

“Breast Cancer: What You Should Know (But May Not Be Told) About Prevention, Diagnosis, and Treatment” by Anne McTiernan – Dr. Anne McTiernan, a renowned breast cancer researcher, provides an informative and accessible guide that covers various aspects of breast cancer, including prevention strategies and treatment options.

“Crazy Sexy Cancer Tips” by Kris Carr – Kris Carr and Sheryl Crow, a cancer survivor herself, Carr shares her personal journey and provides practical advice for women facing cancer. Her book offers insights into coping with the emotional and physical challenges of the disease.

“Bald Is Better with Earrings: A Survivor’s Guide to Getting Through Breast Cancer” by Andrea Hutton – Written by a breast cancer survivor, this book is a candid and often humorous account of the author's journey through diagnosis, treatment, and recovery.

"Cancer Hacks: A Holistic Guide to Overcoming Your Fears and Healing Cancer" by Elissa Goodman – This book offers a holistic approach to dealing with cancer, emphasizing nutrition, mindset, and lifestyle changes that can complement traditional medical treatments.

"It's Not About the Bra: Play Hard, Play Fair, and Put the Fun Back into Competitive Sports" by Brandi Chastain and Daniel Paisner – This book by soccer star Brandi Chastain discusses her experience with breast cancer and her determination to stay active and positive throughout her treatment.

Interesting Podcast

The Doctor's Art Decoding Cancer (with Dr. Harold Varmus)

12.

MENOPAUSE AND AGING

STUDENT LEARNING OUTCOMES

At the end of this chapter you should be able to:

- Describe the terminology of menopause and discuss why it is confusing
- Explain the physiological changes that occur during the menopausal transition
- Recall the different ways in which the MT impacts a woman's health
- Describe hormone replacement therapy
- Discuss agism and the double standard women are held to
- Recall the hypothesis on how aging is controlled at the cellular level
- Explain why lifestyle choices during mid-life are the key to healthy aging

Menopause is perplexing.

Why can this part of a woman's life be so confusing? First, there are so many different phrases and ways to refer to menopause. Some call it "the change", others say it is a woman's "midlife crisis", or in a more positive light, "second spring". But there are also confusing terms such as premenopause or perimenopause.

Second, a woman is not always certain that menopause has happened and women often do not know what to expect during this time of their lives. During this transitional period of life, a woman may experience a wide variability in symptoms and she often does not know that it is happening until it is well over. A survey of nearly 1,000 women regarding their attitudes toward menopause revealed much confusion, uncertainty, and dread (Harper et al. 2022). Part of this is due to the confusing terminology used to describe the different phases of this period of a woman's life.

Ambikairajah, Walsh, and Cherbuin (2022) review menopause terminology. The **menopause transition** (MT) is the period **before** the final menstrual period (**FMP**). It is during MT when variability in the menstrual cycle is increased. Missing at least one menstrual period within the past 3 months or a variation in menstrual cycle length of 7 days or more defines the early MT. However, nearly one-fourth of women report very little change in their cycles before they stop menstruating (Hale, Robertson, and Burger 2014).

There is also what is known as **perimenopause** (a specific phase overlapping MT) which is the period immediately before the FMP when endocrinological, biological, and clinical features of approaching menopause commence, as well as the first year after menopause. Then there is **menopause**, the period after 12 consecutive months of amenorrhea. In other words, a woman has not yet actually experienced menopause until they have stopped having their period for a full year. Therefore **menopause can only be known after the fact**, a year or more after the the FMP. And postmenopause is referred to as the period following the FMP. FSH levels continue to rise while estrogen continues to fall until they stabilize approximately two years after the FMP (Harlow et al. 2012).

- **The official definition of menopause** = The WHO specifically defines menopause as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity and deemed to have naturally occurred after 12 consecutive months of amenorrhea, for which no other obvious pathological or physiological causes could be determined.
    - Induced menopause, is defined as the cessation of menstruation following either surgical removal of both ovaries (i.e. oophorectomy), or iatrogenic ablation of ovarian function (i.e. chemotherapy or irradiation). The result is irreversible loss of fertility

(Ambikairajah et al. 2022).

Traditionally women have not usually discussed menopause, nor have they received the support needed from healthcare providers, family, or friends during this transition. A lack of education for women and understanding or empathy from their general practitioners can exacerbate their feelings of confusion and isolation (Harper et al. 2022). It is also important to bear in mind that some transgender men and non-binary or gender-diverse people might also experience menopause and are also in need of support.

When does the MT happen?

In 2001 and 2011 members of the Office of Research on Women's Health (ORWH) of the National Institutes of Health, The North American Menopause Society (NAMS), the American Society for Reproductive Medicine (ASRM), the International Menopause Society (IMS), and the Endocrine Society came together for the Stages of Reproductive Aging Workshop (**STRAW**). They were tasked with reviewing the available research and providing "consistent classification of menopause status for studies of midlife women" (Harlow et al., 2012).

STRAW produced a **chronology of the ovary** with stages that go from menarche at -5 to peak reproductive, -4, to late reproductive, -3, to -2 early MT, -1 late MT, 0 FMP, +1 early post-menopause and then +2, late post-menopause. The MT, FMP, and PM stages are illustrated in the figure below.

Early MT is often characterized by missed periods and fluctuations in FSH. Pre-ovulatory LH surge is diminished (downs) suggesting that the hypothalamus does not respond normally to estrogen. The late MT period is characterized by more consistently elevated FSH, and amenorrhea ≥60 days. **Late MT** lasts approximately 1 to 3 years (Santoro 2005). The aging of the ovary is synced with the chronological aging of the individual. Together, they influence the pace of the menopausal transition process and how long it lasts (Talaulikar 2022).

STRAW chronology of the ovary from early menopause transition (MT) to post-menopause (PM) characterized by changes in FSH levels. Image adapted from Ambikairajah, Walsh, and Cherbuin (2022).

What triggers the MT?

Depletion of oocytes due to hormonal shifts triggers MT. Each woman has a "threshold' of oocytes below which normal ovarian function cannot be maintained" (Davis et al. 2023). This usually occurs in women over 45 years of age and can last five years or more. As the threshold approaches, inhibin declines which leads to a rise in FSH especially in the early follicular phase of the cycle which shortens the follicular phase and ramps up the follicle maturation process. The follicles appear larger but have a slower growth rate, resulting in smaller follicles being released during ovulation (Santoro et al. 2021; Davis et al. 2023). As the number of follicles decreases, longer spans of amenorrhea occur, and the late MT can be marked by more noticeable symptoms of hot flashes (VMSs), sleep issues, vaginal dryness, and mood swings. The MT can last four years or more.

Can one confirm the MT?

A single test for MT does not yet exist. However, the level of FSH can be measured if a woman is not on any type of hormonal birth control. Elevated early follicular phase FSH levels are supportive criteria for entry into STRAW stage −2, and FSH levels of >25 IU/L were also included as a supportive criterion for entry into stage −1 (Harlow et al., 2012). However FSH levels can fluctuate and are not always reliable therefore clinicians usually rely on a combination of menstrual history, age, and symptoms (Bastian, Smith, and Nanda 2003).

Perimenopause-Menopause-Postmenopause, how to know?

One of the largest and longest studies examining the menopause transition (MT) is the Study of Women's Health Across the Nation (SWAN). This study began in 1996 as a multisite, multiracial/ethnic, longitudinal project examining 3,302 women (42 and 52 years of age). All participants had an intact uterus and at least one ovary, were not receiving hormone therapy, were not pregnant or lactating, and had at least one menstrual period in the 3 prior months. The results of this long-term project are summarized in the textbox below. These results have been, and are continuing to be published. Thus far the combined results show that MT is much more than not having one's period anymore, the changes associated with it have far-reaching effects.

Summary of SWAN findings (El Khoudary et al. 2019)

Menstrual cycle length and the onset of MT

- Menstrual cycle length increased beginning 7.5 years before the FMP
- Amenorrhea of 60+ days is the marker of entry into the late stage of the MT
- Smokers have both an earlier onset of the MT and a shorter total MT duration
- Black women have a longer total MT duration

Age at natural menopause

- The median age at natural menopause was 51.4 years

- Familial predisposition to early or late menopause is commonly encountered, which supports the hypothesis of genetic programming of ovarian failure

Hormonal shifts

- Estrogen (E2) and FSH levels fall and rise respectively
- Patterns of E2 declining and FSH rising were observed but not all women experienced a single pattern
- Levels of circulating E2 and FSH varied by body mass index (BMI) and race/ethnicity

Vasomotor symptoms (VMS), defined as hot flashes and night sweats

- Up to 80% reported experiencing VMS
- Black women had the highest prevalence and longest duration of VMS and were most bothered by their VMS
- Women in lower socioeconomic positions were more likely to have VMS, independent of race/ethnicity
- Frequent VMS persisted for a median of

7.4 years, with even longer durations for some women
- Recent research also links VMS to poorer cardiovascular health (Thurston 2023)

Sleep difficulties

- Increased trouble sleeping reported in perimenopausal women
- Compared to other ethnic groups, White women reported the most sleep problems and Hispanic women the least

Depression and anxiety

- Greater likelihood of experiencing high depressive symptoms in the early peri-, late peri-, or postmenopause, as compared to the premenopause
- Greater likelihood of experiencing high anxiety symptoms in the early peri-, late peri-, and postmenopause compared to premenopause; peaking in late perimenopause

Memory loss

- A temporary decline in both processing speed and verbal episodic memory during perimenopause
- The decline resolves in postmenopause

Cardiovascular health

- Sharp increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein (Apo)B levels within a 1-year interval surrounding the FMP
- Acceleration in LDL-C was associated with a greater risk of carotid plaque later in life in a follow-up analysis

Vaginal dryness

- Vaginal dryness and atrophy increased across the MT, from about 19% in pre-and early perimenopause to 34% in postmenopause years

Bone density loss

- Noticeable decline in BMD (bone mass density) – 2 years before the FMP
- A drop in estrogen is one of the triggers of

the greater- bone- turnover -greater-bone-loss cascade

- The rate of BMD loss commences at about 2 years post-FMP
- Cortical bone remodeling also begins 1 year before the FMP
- Fracture rates for White women are double that of Black and Asian women in the United States

Hot flashes explained

Hot flashes, or Vasomotor Symptoms (VMS), are defined as "transient periods of flushing, sweating, and a sensation of heat, often accompanied by palpitations and a feeling of anxiety sometimes followed by chills" (Kronenberg 1990). The exact cause of VMSs is yet to be completely understood. However, the underlying cause is associated with problems in the hypothalamus, the body's thermoregulation center, and specifically hypothalamic neurotransmitters whose impaired functionality is tied to estrogen depletion (Talaulikar 2022).

During a VMS event, blood flow increases concurrent with increased body temperature in the upper torso region. The body responds with an increase in peripheral blood flow (vasodilation) to lose heat resulting in chills that bring the body temperature back to normal (Bansal and Aggarwal 2019).

Osteoporosis

Osteoporosis, the most common type of bone disease, is caused by low bone mass and the disruption of bone microarchitecture can significantly increase the risk of bone fractures. Due to age-related changes primary osteoporosis usually occurs in people aged 50 years or above. Both women and men can be affected by osteoporosis, however, the decline in estrogen and progesterone during menopause significantly increases the risk of the disease. It is associated with a diminished quality of life (Ji and Yu 2015).

Sözen, Özışık, and Başaran (2017) describe the connection between menopause and osteoporosis. Bone remodeling involves the resorption of old or damaged bone, followed by the deposition of new bone material, and there is a balance between bone tissue loss by resorption and bone tissue formation. When resorption is greater than formation, bone is lost and this starts happening after puberty. Multiple factors determine the rate of bone remodeling and loss including genes, nutrition, overall health, and physical activity. Estrogen is a fundamental participant in bone remodeling and when it declines during MT this results in an imbalance in bone remodeling, thereby increasing the risk of fracture.

How is osteoporosis diagnosed?

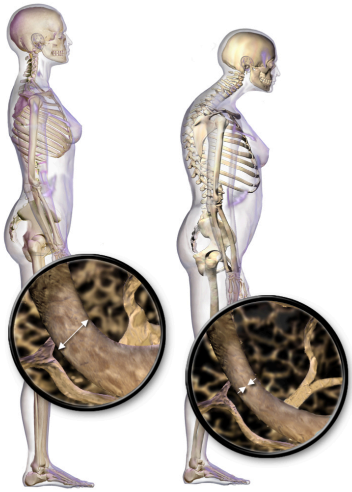

Illustration depicting healthy bone structure and standing posture on left and osteoporosis on right. Image by Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014" WikiJournal of Medicine

According to Sözen, Özışık, and Başaran (2017), the WHO criterion for osteoporosis is based on the T-score. This score is determined from the results of a bone mineral density test (BMD) obtained by a central dual-energy x-ray absorptiometry (DXA) that uses radiation to measure the amount of calcium in a specific area of bone, usually the femoral neck and lumbar spine (Ji and Yu 2005). T-score values between -1.0 and -2.5 are osteopenia (weakened bones), and a T-score value of -2.5 or lower is osteoporosis.

Prevention and treatment of osteoporosis

Calcium and vitamin D (V-D) is essential for bone formation therefore adequate intake of calcium and V-D, are key aspects for prevention and treatment. The Food and Nutrition Board

(FNB) recommends 1,200 mg/day UL calcium for women 51+ years of age. (Institute of Medicine 2011). Regular weight-bearing and muscle-strengthening exercises are also important for the maintenance of bone density. Not all exercises are equal in their ability to ward off bone loss. Benedetti et al. (2018) found that strength training involving specifically the neck of the femur and at the lumbar spine for a minimum of 3x/week along with resistance training for the lower limbs to be most effective.

The two main prescription medications for osteoporosis are the antiresorptive agents known as bisphosphonates (BPs) e.g. Boniva, and estrogen therapy (MRT). BPs are considered a first-line-treatment and have been widely prescribed over the years to maintain BMD in the neck and spine (Compston, McClung, and Leslie 2019). MRT is highly effective at stopping bone loss and preventing fractures (Ji and Yu 2005).

Treatment for menopausal symptoms

For some women their menopausal associated symptoms are minimal and they do not require any treatment. However, for others, the symptoms can be disruptive and debilitating. Even though 84% of women surveyed (out of a total of 6,096) experienced at least one symptom with 45% noting their symptoms to be a problem (Rymer and Morris 2000), “over 85% of women in high-income countries do not receive effective, regulator-approved treatment for their menopausal symptoms" (Davis et al. 2023).

Non-prescription treatments

Although over-the-counter remedies may be more affordable and seemingly "natural" they are not regulated by the FDA and their true efficacy is questionable. Studies have been conducted on the following:

- Phyto-estrogen supplements were not effective beyond what is achieved with a placebo (Chen, Lin, and Liu 2015).
- Rheum rhaponticum (Er 731) extract was found to help reduce hot flashes (Heger et al. 2006).
- Acupuncture was found to be ineffective for hot flashes (Dodin et al. 2013).

Prescription medication for VMS

- The FDA just approved Veozah (Fezolinetant) as a non-hormonal treatment for moderate to severe VMS in menopause. According to Shaukat et al. (2023) Veozah "targets the disrupted thermoregulation underlying VMS. It modulates neural activity within the thermoregulatory center by crossing the blood-brain barrier, offering relief from hot flashes and night sweats".

Anti-depressant treatments

- For feelings of depression and anxiety associated with MT, anti-depressants are often prescribed and " can offer some relief for many women, none are as effective as menopause hormone therapy, and side effects such as sexual dysfunction are not uncommon" (Davis et al. 2023).

Menopause Hormone Therapy (MHT) aka HT or HRT

Many of the symptoms (eg. hot flashes, bone loss, vaginal dryness) are due to a depletion of estrogen therefore systemic estrogen therapy can alleviate those problems. "Estrogen replacement remains the most effective treatment for VMS" (Hamoda et al. 2020). The form of estrogen needed is estradiol which can be taken via transdermal patch, gel, or spray or as an oral pill. For those who still have a uterus, uterus progesterone must also be taken concurrently to protect from endometrial cancer. Those who have had a hysterectomy can take just estrogen and do not have to worry about the problems associated with the endometrium.

There are likely cardiovascular health benefits associated with taking MRT as soon as symptoms arise, usually around age 45, because it is thought that the beneficial effects of MHT are dependent on the prevention of atherosclerosis before plaque forms as opposed to in older women who already have plaque in their blood vessels (Naftolin et al. 2019).

Confusion around MHT from the WHI studies

Two major clinical studies conducted in the 1990s under the Women's Health Initiative (WHI) put a negative spin on MRT that has lasted for decades. Natari et al. (2021) reviewed the impact of the published results (WHI 2002, WHI 2004) on the perception of the safety of MRT. One study on HT use by women with an intact uterus (WHI 2002), and the other on ET use by women with a hysterectomy (WHI 2004) both terminated early because of increased breast cancer (WHI 2002) and increased stroke (WHI 2004). Widespread negative media coverage led to a significant worldside rapid decline in HT use. Yet further investigation uncovered problems with the data and a "reanalysis found that both studies were confounded by age with a 'window of opportunity' for cardiovascular health benefits if HT was initiated before 60 years or within ten years of menopause" (Natari et al. 2021). Subsequent investigations have shown CVD and cancer mortality did not differ between the hormone therapy and placebo arms in both WHI studies and the guidelines for MHT have been recently updated to reflect more recent findings (Davis et al. 2023). Furthermore, the excess risk associated with breast cancer is attributable to the use of combined (estrogen + progesterone) treatments, not estrogen-alone therapy (Vinogradova, Coupland, and Hippisley-Cox 2020). The duration of therapy should be based on each individual's symptoms and personal benefit-risk evaluation.

The takeaway from the MT

Think of menopause as "a bridge to the most vital and liberated period in a woman's life" (Sheehy 1998). This is a natural period of a woman's life with big changes that can have consequential health ramifications. Heading into MT women need to be prepared and open to discuss the changes their bodies experience. This is also a time when one needs to focus on optimizing their health because it is "the gateway to healthy aging for women" (Davis et al. 2023).

> Women, our bodies change drastically in comparison to men. We're going through menopause. We've got a lot going on, and I don't think we've done enough to understand what aging means for women's bodies: What are we supposed to look like? How are we supposed to feel? We're not talking about that enough. I'm 56 with a 56-year-old-body, and I love my body. – *Michelle Obama*

Aging

You cannot live without aging

We are often afraid of getting old because of the unnatural emphasis by the media and culture on youth. Social media, advertising, television, movies, and print media create an unrealistic ideal of permanent youth and beauty. Saucier (2004) comments “women are constantly bombarded with visual images of young women and ads promising youthful looks forever.” In the United States a culture of ageism, especially against women, remains (Chrisler, Barney, and Palatino 2016). The well-known notion of a ‘double standard of aging’ coined fifty years ago by famed author Susan Sontag (Sontag 1972) suggests that an aging woman is judged more harshly than an aging man persists and must be changed. As women enter middle age, the physical changes in their appearance can be striking and they need help in acknowledging changes…and dealing with the emotions associated with these changes (Saucier 2004). We must embrace old age and recognize the significant contributions older women make to society. Dolly Parton speaks on aging as something to not personally focus on: “I don’t think about my life in terms of numbers. First of all, I ain’t never gonna be old because I ain’t got time to be old. I can’t stop long enough to grow old.”

Humans are fortunate compared to their wild counterparts who typically do not live long enough to get old. Aging is accompanied by gradual changes in most body systems. Defined as “a progressive loss of function accompanied by decreasing fertility and increasing mortality” (Kirkwood and Austad 2000). There is a a great deal of variability in aging with some people living relatively independently into their 90s and others living not as long. The average life span of a woman in the United States is 79 years (Arias et al. 2022). In general, women live longer than men whose average life span is 72 years. This gender gap in life expectancy is due to both biological and sociocultural factors.

The process of aging is complex and not yet understood. A network of genes and epigenetic controls along with environmental impacts affect aging (Pal and Tyler 2016).

There are three main hypotheses regarding aging

1. **Senescence hypothesis** – Senescence, long-term cell-cycle arrest, occurs due to excessive intracellular or extracellular stress or damage. This can be due to random mutations accumulating over time, or through continued shortening of chromosomes through replication, eventually depleting our capacity for maintenance and resilience (Dodig, Čepelak, and Pavić 2019). The dominant explanation for this is a DNA replication-dependent shortening of telomeres (Ogrodnik 2021).

2. **Somatic mutation hypothesis** – the life span is limited by cancer rather than a loss of functionality and the cancer is a result of mutations in somatic cells (Wolf 2021)
3. **Program hypothesis** – aging is regulated by a biological clock with specific "genetic mechanisms regulating the pace of aging" (de Magalhães and Church 2005).

Addressing the challenges and opportunities presented by an aging global population is necessary. A national census report (2020) found a 36% increase in people aged 65 and older over the past decade, with the older population growing five times faster than the total population. The potential to improve health and well-being, reduce the burden of age-related diseases, and enhance the overall quality of life for older individuals lies within gaining a better understanding of the aging processes. Additionally, further research in the biology of aging can inform policies and practices that benefit both individuals and society as a whole. However, aging happens and it is important to acknowledge that does not need to be medicalized. Rather a focus on healthy aging, emphasizing preventive measures, lifestyle choices, and healthcare practices that promote well-being and independence in later life is important.

What is healthy aging?

As Applewhite (2020) points out "we tend to think of aging as something sad that old people do, when in fact we are aging from the minute we are born." Healthy aging is the ability to maintain a high quality of living throughout your life by optimizing opportunities to maintain physical and mental health and independence. Working toward healthy aging needs to begin by middle age. Research indicates that the mid-life period is a "window of opportunity" to maintain and establish positive health behaviors (Cann 2009). These four things have been shown to make a difference in how we experience old age:

- smoking cessation
- a healthy diet (Mediterranean diet is recommended (Fincelli et al. 2022))
- regular physical activity
- staying connected to others

As women age it is important to stay mentally active and exercise, continue to make smart food choices, be cautious with alcohol, keep on schedule with regular check-ups, prioritize mental health, and avoid isolation. Loneliness can be especially debilitating to women's health (Thurston and Kubzansky 2009) and a quarter of individuals 65 and older "are considered to be socially isolated, and a significant proportion of adults in the United States report feeling lonely" (National Academies of Sciences, Engineering, and Medicine 2020).

Dementia and Alzheimer's Disease in Women

Memory loss may occur as one ages, with most individuals beginning to notice mild memory loss after 65 years. When the memory loss is serious enough to interfere with daily life it is known as dementia. Alzheimer's disease is the most common cause of dementia in aging" (Buckner, 2004). It is a "progressive, neurodegenerative disease characterized by loss of function and death of neurons in several brain areas, leading to decline of mental functions prominently including memory.

Older women appear to be at greater risk of developing dementia and Alzheimer's disease (AD dementia) than men. Ronquillo et al. (2016) examined data from 24,270 patients and found that "females were 1.5 times more likely to have a documented diagnosis of probable AD than males."

Meilke (2018) notes several possible reasons why women are more susceptible than men.

- For instance, it may be related to the greater immune response mounted in women where higher levels of amyloid are deposited in women's brains to resist infection with the formation of amyloid plaques as a byproduct.
- A diagnosis of midlife depression is correlated to an increased risk of AD dementia and women have double the risk of depression when compared to men.

- There is a link between menopause and AD. Shceyer et al. (2018) point out that estrogen is important in brain function because it is involved in intracellular signaling, neural circuit function, and energy availability and therefore as estrogen levels change during the menopause transition modifications in the brain can occur. Interestingly Kim et al. (2022) observed a lower risk of dementia in women who used estrogen replacement therapy (HRT) to relieve menopausal symptoms (including depression). Brinton proposed the "healthy-cell bias hypothesis" stating that estrogen replacement initiation impact depends on the health of a cell. Therefore the timing of HRT initiation is critical with women receiving greater benefits when taking HRT closer to the age of menopause. This is thought to be because in younger women "neurological health is not yet compromised" and thus there would be a lower risk of AD dementia (Brinton, 2008).

In a recent study of women who used a combination of estrogen and progestin HRT, the rate of AD dementia increased (Pourhadi et al., 2023). However, when examining the timing and formulation of HRT support for the use of estrogen in younger women was found. Nerattini et al. (2023) conducted a meta-analysis of 21,065 treated and 20,997 placebo participants and 45 observational reports (768,866 patient cases and 5.5 million controls), and found "mid-life estrogen therapy use was associated with a 32% reduction in dementia risk, while estrogen-progestin was not associated with a reduction in dementia risk. Conversely, late-life use of both formulations was associated with increased dementia risk, more so with EPT than ET, although neither reached statistical significance." Although it appears that ET given during midlife can reduce dementia, the authors note the need for an "individualized approach to HT usage to increase safety and predictive efficacy for AD prevention" that would take into account a cost-benefit analysis of ET for each woman depending on various factors (Nerattini et al., 2023).

Q&A with Dr. Roberta Diaz Brinton, PhD.

Dr. Roberta Diaz Brinton, Ph.D.

Director, Center for Innovation in Brain Science

Regents Professor Pharmacology, Neuroscience, and Neurology

College of Medicine, University of

Arizona

What drew you to research the brain and specifically Alzheimer's in women? The journey to devoting a great deal of my research to Alzheimer's disease in women began with an encounter with one woman with Alzheimer's disease. This fortuitous encounter with one woman with Alzheimer's disease transformed the scientific journey of this one woman neuroscientist, me. The decision to focus a great deal of our research effort on understanding why the female brain was strongly influenced by the fact that women have a twofold greater lifetime risk of developing Alzheimer's disease. My reasoning was if that we understood why the female brain was at greater risk for developing Alzheimer's disease I could, at the very least, address the majority of persons who would develop the disease. In parallel, we would learn a great deal about the disease that could inform us about the mechanisms driving the disease in the male brain. To date, our research over the past several decades has taught us that the greater risk of developing Alzheimer's disease is not because women, on average, 4.5 more years than men. Rather, it is because the disease can begin earlier in women during the midlife endocrine aging transition of the menopause. Importantly, we have discovered the key drivers of the increased risk of Alzheimer's disease in women and have developed therapeutic strategies to address these processes to sustain brain health and function throughout midlife and beyond. Along the way, we have made discoveries that led to the first therapeutic to regenerate the Alzheimer's brain which is currently in Phase 2 clinical trial in both women and men who carry the APOE4 gene and who are at greatest risk for the disease.

What do you like most about your career? I feel incredibly fortunate to be both a discoverer and for the opportunity to conduct what I call 'real science that really matters. In my case, it is the opportunity to discover the magnificence of the brain and through that understanding address a critical unmet need – a cure for Alzheimer's disease. I very much enjoy the collaborative endeavor of our scientific research which includes exceptional minds with different intelligences from different life experiences and cultures.

In addition to being a renowned researcher, you are also the Director of the Center for Innovation in Brain Science at U. of Arizona. What is it like to juggle research with being the leader of this important center? It is challenging but with the exceptional Center for Innovation in Brain Science team, every day is a joy to be with them while we collectively take on the challenge of developing cures for Alzheimer's, ALS, Multiple Sclerosis and ALS.

What advice do you have for future women scientists? You are already leading the most important member of your team – You. The way you lead you is the way you will lead others. Learn how to effectively lead you. What works and what doesn't work. You are here for a purpose – really. Lead you to that purpose.

Aging comes with its share of challenges, however many individuals can age gracefully by focusing on self-care, maintaining social connections, and cultivating a positive attitude. Seeking support from healthcare professionals, friends, and family can also help individuals navigate the physical and emotional changes that come with aging. It's important to recognize that aging is a natural part of life, and there is no one-size-fits-all approach to aging gracefully. Each person's journey is unique, and the key is to find strategies and practices that work for one's circumstances and well-being.

Think, Pair, Share

What do you know about menopause and from whom/where did you learn about this topic?

How might socioeconomic factors contribute to menopausal symptoms?

What are some factors that contribute to the aging of a cell?

Why is it important to adopt and maintain a healthy lifestyle when a person is young?

What reasons besides the fact that women tend to live longer than men would contribute to the increased incidence of AD dementia in women?

Deeper Questions

Would it be a “perfect world” if humans did not age?

Hot flashes do not cause any real medical issues so why should women get treatment for them?

Has society’s perception of menopause evolved? and what cultural, social, and medical factors have influenced these changing attitudes towards this natural stage of a woman’s life?

To what extent is it scientifically feasible and ethically justifiable to pursue interventions aimed at reversing the aging process in humans, and what are the potential societal, economic, and individual implications of such endeavors?

Key Terms

- Aging
  - Alzheimer’s
  - BMD
  - FMP
  - Induced menopause

MT
MRT
Menopause transition
Perimenopause
Premenopause
Postmenopause
Osteoporosis
Osteopenia
T-score
VMS

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Suggested Readings

"The Wisdom of Menopause: Creating Physical and Emotional Health and Healing During the Change" by Christiane Northrup, M.D. – This book provides a holistic approach to menopause, discussing not only the physical changes but also the emotional and spiritual aspects of this life transition.

"Menopause Confidential: A Doctor Reveals the Secrets to Thriving Through Midlife" by Tara Allmen, M.D. – Dr. Tara Allmen offers practical advice, expert medical insights, and empowering information to help women navigate the menopausal journey with confidence.

"Goddesses Never Age: The Secret Prescription for Radiance, Vitality, and Well-Being" by Christiane Northrup, M.D. – This book explores the concept of aging gracefully and maintaining vitality throughout life.

"This Chair Rocks: A Manifesto Against Ageism" by Aston

Applewhite – Applewhite describes the roots of ageism in history and how it divides and debases

"Aging Backwards: Reverse the Aging Process and Look 10 Years Younger in 30 Minutes a Day" by Miranda Esmonde-White – While not focused solely on menopause, this book offers exercise and lifestyle strategies to promote flexibility and strength as we age.

"The Longevity Paradox: How to Die Young at a Ripe Old Age" by Steven R. Gundry, M.D. – Dr. Steven Gundry delves into the science of aging and offers dietary and lifestyle recommendations to promote healthy aging.

"Women's Bodies, Women's Wisdom: Creating Physical and Emotional Health and Healing" by Christiane Northrup, M.D. – This comprehensive guide covers various aspects of women's health, including menopause, and provides insights into holistic well-being.

Interesting Podcast

Not your mother's menopause with Dr. Fiona Lovely The State of Women's Health Care at Midlife, the Menopause Summit Interview